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CLINICAL USE OF HEPARIN IN THE PERITONEUM FOR THE PREVENTION OF ADHESIONS

REPORT OF FOURTEEN CASES

EDWIN P. LEHMAN, M.D.

AND

FLOYD BOYS, M.D.

CHARLOTTESVILLE, VA.

In 1940 we presented two papers [1] on the use of heparin in the prevention of peritoneal adhesions in the dog. In these reports it was shown that the reformation rate of adhesions after the intraperitoneal administration of effective doses of heparin was in the neighborhood of 30 per cent, while the average reformation rate among controls was 147 per cent. Since the publication of these papers, laboratory experimentation has been continued, and an extensive series of experiments will be reported elsewhere. It can be stated here that these experiments confirm the conclusions in the reports of our earlier work. It is our opinion that this method of diminishing the number of reformed adhesions after division is theoretically sound, and it has been proved to be practically effective in the dog.

The mechanism of this effectiveness is believed to consist in the diminution of the coagulability of the serous exudate which is the first response of the peritoneum to injury. "The process of organization always takes place in fibrin, and cannot take place without fibrin. It seems logical, therefore, to expect that the prevention of the formation of fibrin will prevent the organization that is the essential element of a permanent pathologic nature." [1a]

To the action of heparin in preventing the coagulation of the exudate is added of course its action in preventing the deposition of fibrin in the cut ends of blood vessels. Without adequate hemostasis it is obvious

From the Department of Surgery and Gynecology of the University of Virginia and the University of Virginia Hospital.

1. Lehman, E. P., and Boys, F.: (*a*) The Prevention of Peritoneal Adhesions with Heparin: An Experimental Study, Ann. Surg. **111**:427-435, 1940; (*b*) Heparin in the Prevention of Peritoneal Adhesions: Report of Progress, ibid. **112**:969-973, 1940.

that the use of heparin in the peritoneum will be associated with intra-abdominal hemorrhage. Until this fact was realized there were a number of deaths from this complication among the experimental animals. After more scrupulous efforts were made to control all oozing points before the introduction of heparin, this danger apparently ceased to exist. There have been as many as seventy-five consecutive applications of heparin to the peritoneum after the division of adhesions in the dog with no bleeding whatever.

The experimental studies just summarized were of course directed toward ultimately trying the method on human beings, provided it could be made safe. During recent months 14 patients have been treated with heparin given intraperitoneally after the division of adhesions. Seven of these patients were treated under our supervision; the others were treated at the different clinics indicated in the protocols.

Various surgeons cooperated by using this method and by furnishing abstracts of their cases.

This report is the first on the clinical use of heparin for the prevention of the reformation of intraperitoneal adhesions.

In an earlier paper [1a] we pointed out that an enormous number of patients must be treated with heparin before a sufficient number will have come to relaparotomy or autopsy to provide a basis for judging the efficiency of the method. Since we still hold this opinion, it is obvious that in the present paper we can make no claims for the effectiveness of the method in the human being. We present the data contained herein to throw light on the safety and the dangers of the method and to put before the medical profession a probably adequate technic for the intraperitoneal administration of heparin in properly selected cases.

INDICATIONS AND CONTRAINDICATIONS

Until greater experience has been had in clinical application, the use of heparin should be limited to cases of acute partial or complete intestinal obstruction due to adhesions and particularly to cases in which previous operations have been performed for obstruction or repeated threatening attacks. In other words, heparin should be used only in that group of desperate cases in which one is willing to accept the hazard of an insufficiently tried method in preference to a future risk of significant proportions.

The one important and essential contraindication to the use of heparin in the abdomen is the presence of an oozing peritoneum after adhesions have been divided. A recent experience hereinafter reported leads us to the further conclusion that heparin should not be used when granulation or subacute inflammatory tissue is present whether hemostasis seems complete or not.

TECHNIC

Before operation, the pulse rate, the erythrocyte count, the percentage of hemoglobin, the systolic and the diastolic blood pressure and the blood coagulation time must be recorded. These determinations must be made every two hours for at least six hours after each administration of heparin and immediately before the next administration. The first four of these are of importance in detecting possible intraperitoneal hemorrhage after the use of heparin. As the drug is absorbed into the blood stream from the peritoneum to some degree, determination of the coagulation time is indicated. The apex of the curve of increased blood coagulation time is reached about two hours after the administration of heparin.

After the usual operation for the division of adhesions, which is performed with as little additional trauma to the peritoneum as possible, and after complete hemostasis of the peritoneum, preferably obtained by ligature, the first step in the introduction of heparin can be taken.

A small stab wound is made through the wall of the abdomen near the area of the greatest mass of adhesions. Through this a no. 24 Pezzar catheter is threaded from within out and pulled up snugly against the anterior peritoneum. The abdominal wound is then closed, again with particular care to preserve hemostasis. After the dressings are applied, 10,000 units of heparin [2] in 300 cc. of physiologic solution of sodium chloride is allowed to run by gravity into the peritoneal cavity through the catheter. The catheter is then clamped, and the patient is returned to the ward.

At the end of twelve hours and after proper study, 5,000 units of heparin is instilled through the catheter in 300 cc. of physiologic solution of sodium chloride, and the same amount is given in the same manner and with the same precautions at twelve hour intervals for five additional doses, making a total of 40,000 units administered over three and one-half days. Experiments with animals [1b] have indicated the necessity of continuing treatment for at least three days if the maximum effect is to be expected.

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2. The heparin used in all but 2 of the cases to be reported is the product prepared by the Connaught Laboratories of the University of Toronto for clinical intravascular use. In recent months we have been furnished liquaemin through the courtesy of Hoffmann-Laroche, Inc. In a large number of laboratory trials this has been found to compare favorably with the heparin of the Connaught Laboratories in regard to both effectiveness and nontoxicity. We believe liquaemin is safe for clinical trial in the peritoneum; this is indicated by a recent report (Lam, C. R.: Heparin Administration: Methods and Results in Thirty Cases, Ann. Surg. **113**:1085-1086, 1941) on its successful use in the treatment of intravascular conditions. We have had no personal experience with any other brands of heparin.

Six hours after the last administration of heparin the stylet of the Pezzar catheter is introduced; the catheter is withdrawn, and the stab wound is left to heal. This interval is chosen in order to run no risk of bleeding from the vessels in the stab wound, which might be opened by the withdrawal of the catheter during the period of prolonged blood coagulation time.

If during any postadministration period the ordinary clinical signs of hemorrhage are noted, prompt treatment is indicated. This consists of discontinuance of any further administration of heparin together with immediate massive blood transfusion. Experimental studies in other laboratories [3] showed an immediate neutralization of the action of heparin in the blood by protamine. Evans [4] suggested the clinical use of protamine zinc insulin as an easily available form of protamine, to be covered of course with the proper amount of dextrose to protect the patient from acute hypoglycemia. No reports of the use of this method in the human being have been found. It seems reasonable to expect that in most cases bleeding due to intraperitoneal heparinization can be controlled by transfusion alone since the blood coagulation time is only slightly and transiently elevated.

REPORT OF CASES [5]

CASE 1.—W. W., a Negro man 44 years of age, was admitted to the University of Virginia Hospital in January 1939; the diagnosis was acute appendicitis with abscess of one week's duration. With conservative treatment the palpable mass disappeared, and the patient became afebrile. He was discharged on the eighth day after admission with instructions to return for interval appendectomy.

He was readmitted in March 1940 for this procedure; he presented no history of abdominal complaints during the thirteen month interval.

With the patient under spinal anesthesia, the appendix was removed, and a large number of thick adhesions in the region of the cecum were divided.

Before closing the peritoneal layer, 1,000 units of heparin in 300 cc. of physiologic solution of sodium chloride was placed in the peritoneal cavity. No further use of heparin was made in this case.

The postoperative course was smooth except for a somewhat persistent distention which lasted about four days; this was relieved by gastric suction. The highest blood coagulation time was twelve minutes. There was no evidence of intraperitoneal hemorrhage. The patient was discharged on the eighth postoperative day in excellent condition.

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3. Chargaff, E., and Olson, K. B.: Studies on the Chemistry of Blood Coagulation: VI. Studies on the Action of Heparin and Other Anticoagulants; the Influence of Protamine on the Anticoagulant Effect in Vivo, J. Biol. Chem. **122**:153-167, 1937.

4. Evans, E. V.: The Clinical Use of Heparin in Thrombosis, Virginia M. Monthly **68**:200-203, 1941.

5. Of the 14 cases reported, 7 are from the University of Virginia Hospital, and the remaining 7 are from other clinics.

This was the first tentative use of heparin in the peritoneal cavity. We would not now feel justified in using heparin in such a case. Further, it was given in an amount which, as indicated by later experimental work, is probably inadequate.

CASE 2.—F. R., a Negro man 34 years of age, was first admitted to the University of Virginia Hospital on Oct. 19, 1940. Four years previously he had had an appendectomy performed elsewhere; this had been followed by drainage from the incision for twelve days. On admission he presented a typical picture of intestinal obstruction; this was treated by immediate surgical operation. In addition to an obstructing band in the region of the distal part of the ileum, exploratory operation revealed numerous other adhesions in the right lower quadrant; these were not divided. Convalescence was entirely satisfactory, and the patient was discharged on the thirteenth postoperative day.

He was readmitted four weeks later with another attack of intestinal obstruction of thirty-four hours' duration. Immediate laparotomy was carried out with the patient under spinal anesthesia. Obstruction was found to be due to a fine adhesion between the mesentery and the small bowel. After division of the band the obstruction was relieved. Eleven additional adhesions between loops of the ileum were also divided.

At and after this second operation, heparin was administered according to the technic already described. After operation the highest blood coagulation time was six minutes. At no time were there clinical symptoms or signs of intra-abdominal hemorrhage. The postoperative course was entirely smooth, and the patient was discharged on the thirteenth postoperative day. He was last seen on March 12, 1941; at that time there was no evidence of intestinal obstruction.

This patient was operated on under what we consider sufficient indications and was properly followed after operation.

CASE 3.—A. M., a Negro woman 51 years of age, was first admitted to the University of Virginia Hospital in 1936 and was discharged with a diagnosis of subsiding acute appendicitis. She returned one month later for appendectomy. Numerous adhesions were found in the region of the cecum; these were not disturbed except in so far as the removal of the appendix necessitated their division.

After more than five years of good health, she was admitted for the third time on Nov. 14, 1940 with a typical history of intestinal obstruction of three days' duration. With the patient under general anesthesia, an immediate operation was performed. In addition to two definitely obstructing adhesions others were found uniting the small bowel to itself, to the mesentery and to the large bowel; in all there were about fifteen. The thicker adhesions were divided after double ligation, and the others were divided by sharp dissection; coagulation of the divided ends was done with the high frequency current. The abdominal cavity was entirely dry on closure.

Heparin was given according to the standard technic. The postoperative course gave no indication of intraperitoneal hemorrhage and was altogether uncomplicated. The highest blood coagulation time was less than eight minutes. The patient was discharged in excellent condition on the fourteenth postoperative day.

She was readmitted about three weeks later with obscure abdominal pain in the right flank. Neither the history nor the physical examination nor the roentgen examination suggested intestinal obstruction. During a hospital stay of four days, the symptoms entirely disappeared, and she was discharged. She returned two

months later to the outpatient clinic, reporting that she had had no complaints in the meantime. Examination at this time showed her to be normal.

In this case the use of heparin after a first attack of intestinal obstruction from adhesions is illustrated. If the patient's condition will permit the complete separation of all accessible adhesions, the use of heparin in such a case may be justified.

CASE 4.—C. W., a white man 53 years of age, was first admitted to the University of Virginia Hospital in May 1936. At that time he had a partial intestinal obstruction for which he was treated conservatively with recovery. He had undergone appendectomy twenty-six years previously, and this had been followed by drainage from the wound.

He was well until three days before his second admission on Feb. 11, 1941 with a typical attack of acute intestinal obstruction. After dehydration had been corrected, operation was performed with the patient under spinal anesthesia. There were several adhesions between loops of the small bowel and between the small bowel and the scar of the previous operation. Division of the latter resulted in the release of the obstruction. All other adhesions were divided. Where ligatures were not easily applied, the bleeding points were coagulated with the high frequency current.

Heparin was administered according to the standard technic. The patient showed no evidence of intraperitoneal hemorrhage and experienced a smooth postoperative course except for a brief period of bronchopneumonia which was treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and a superficial wound infection which was practically healed on discharge. The highest blood coagulation time was seven minutes. He left the hospital well on the thirteenth postoperative day.

This is another case in which sufficient indications for the use of heparin were present and in which the postoperative observation was adequate.

CASE 5.—E. H. S., a white man of 60 years, was admitted to the University of Virginia Hospital in 1934 with a history of acute abdominal disease persisting for ten days. There was obstruction of the rectosigmoid due to an inflammatory mass resulting from acute appendicitis. The mass was drained, and a lateral transverse colostomy was performed. After subsidence of the inflammatory process, the colostomy was closed; this left a hernia about 3 cm. in diameter. After this episode, the patient had occasional attacks which suggested partial intestinal obstruction and which were relieved spontaneously or by the use of enemas.

The patient was again admitted on May 19, 1941 with an attack of intestinal obstruction of twelve hours' duration. Relief was obtained with an enema. Within twenty-four hours a much more severe attack occurred which could not be relieved by enema, and operation was advised. On opening the abdomen with the patient under spinal anesthesia, many adhesions were observed throughout the abdominal cavity, including a band which was producing almost complete obstruction of the ileum. After this was divided, numerous other adhesions were separated, and bleeding was controlled by electrocoagulation. Appendectomy was then carried out. In the area of the hernia, no adhesions were disturbed.

Heparin was administered according to the standard technic. There were no signs of intraperitoneal hemorrhage, and the postoperative course was entirely

smooth. The highest blood coagulation time was five minutes. The patient was discharged in good condition on the fourteenth postoperative day.

This patient was advised to enter the hospital for the repair of his hernia within a few weeks after discharge; this would offer the opportunity to check on the effectiveness of heparin treatment in a single case.

CASE 6.—In 1937, A. B., a Negro woman 34 years of age, had undergone laparotomy in which the following procedures were carried out: supravaginal hysterectomy, right salpingo-oophorectomy, left salpingectomy and appendectomy. The postoperative course had been satisfactory.

She was admitted to the hospital on May 5, 1941 with a history of intestinal obstruction persisting for twelve hours. She was immediately placed under spinal anesthesia and operated on. A volvulus in the small bowel was exposed; this was apparently due to peritoneal adhesions. Resection of 2 feet (61 cm.) of the ileum was carried out with end to end anastomosis. The patient made a satisfactory recovery and was discharged on the thirteenth day after operation in excellent condition.

She was readmitted to the hospital on the following day, suffering from a definite syndrome of intestinal obstruction. She was treated conservatively for slightly over twenty-four hours, with temporary relief. At the end of that period, however, it was obvious that obstruction was continuing, and operation was therefore advised.

The abdomen was opened with the patient under spinal anesthesia. Considerable dilatation of the bowel was noted above a point of obstruction 10 cm. proximal to the site of anastomosis, caused by angulation of the bowel from a string adhesion. Division of the latter resulted in relief of the obstruction. Rather extensive separation of the adhesions followed and was associated with marked and persistent oozing from the granulation tissue that had formed after the operation two weeks before. The abdomen was apparently dry on closure, but hemostasis required extensive electrocoagulation.

Heparin was administered according to the standard technic at the time of operation. The first and second postoperative doses also were given. On the morning of the second postoperative day, the patient suddenly went into shock and died. The highest blood coagulation time was seven minutes. On account of an unfortunate oversight, the usual and essential postoperative studies of the red blood cells, the hemoglobin and the blood pressure were omitted. The only hint of impending disaster was an elevation of the pulse rate to 130 during the afternoon of the first postoperative day, associated with an elevation of temperature. This was ascribed to the common postoperative reaction after so extensive a procedure. No transfusion was given.

Autopsy revealed a large amount of fluid blood in the peritoneum, containing large clots; other observations were not related to the patient's death. The exact source of hemorrhage could not be determined.

In this case occurred the only death known to have followed the intraperitoneal use of heparin. In retrospect it is believed that the administration of heparin was definitely contraindicated in the presence of the extensive oozing from subacute inflammatory tissue, which was controlled with difficulty. It is also obvious that the patient had entirely inadequate postoperative observation. In view of the relatively slight elevation of the blood coagulation time, there is every reason to think

that one or two massive transfusions would have saved her life if the diagnosis of intraperitoneal hemorrhage had been made. This case will be further discussed later.

CASE 7.—O. S., a Negro man 65 years of age, was admitted to the University of Virginia Hospital on March 19, 1941 with a diagnosis of acute intestinal obstruction of thirty-six hours' duration without previous abdominal complaint. Immediate exploratory operation revealed numerous adhesions in the region of the appendix with fixation of one loop to the posterior abdominal wall. Since this was the first attack, heparin was not used. The patient was discharged from the hospital on the twelfth day after an entirely smooth convalescence.

He returned to the hospital on July 2 with recurrent obstruction. After four hours of medical treatment, operation revealed apparently more adhesions than had been present at the first procedure. About ten loops of bowel were involved. After complete freeing of adhesions and careful hemostasis, the abdomen was closed, and heparin was administered by the standard technic.

During the first twelve hours after operation the pulse rate rose to 130, and the systolic blood pressure dropped from 140 to 105. During this time the erythrocyte count and the hemoglobin content remained stationary at the preoperative level. The coagulation time during this period rose from three to five and one-quarter minutes. After the second dose of heparin, twelve hours after operation, the systolic blood pressure remained in the neighborhood of 125, with a slight drop seven hours later. During this period the red blood cell count had dropped from 5,200,000 to 4,000,000 and the hemoglobin content from 87 to 70 per cent. The third dose of heparin was therefore not given. Except for moderate ileus, the patient did well for the next two days. On July 5, however, it was found that the erythrocyte count had dropped to 2,500,000 and the hemoglobin content to 58 per cent. The patient was therefore given a transfusion; two more transfusions were given before discharge which occurred on the fourteenth day with the patient in excellent condition.

Although it is possible that the oozing continued for forty-eight hours after the last administration of heparin, it does not seem probable in the face of a normal coagulation time. Furthermore, no blood appeared in the inlying catheter, and the highest icteric index measured on several postoperative days up to the tenth was 11.

The case illustrates the proper management in cases of suspected intra-abdominal hemorrhage.

CASE 8.—Miss G., a white woman aged 40, was operated on by Dr. Warfield M. Firor at Johns Hopkins Hospital, Baltimore, on July 15, 1940. She had already undergone numerous operations with the division of extensive adhesions.

At the last operation many adhesions around the sigmoid and the cecum were divided without bleeding. A small catheter was inserted through a stab wound, and 10,000 units of heparin in 100 cc. of physiologic solution of sodium chloride was given at the close of the operation. This dose was repeated at twelve, thirty-six and forty-eight hours after operation. Six hours after operation there was a pinkish discharge around the tube, and subsequently a small hematoma developed in the wound. Otherwise the postoperative course was smooth without further evidence of bleeding. The bleeding time and the blood coagulation time remained within normal limits. The patient was free from symptoms of intestinal obstruction for at least six months after operation.

CASE 9.—B. K., a white woman 45 years of age, was operated on by Dr. James C. Owings at the Baltimore City Hospitals on Aug. 23, 1940. She had undergone six operations between the ages of 10 and 28 years: (1) at 10 years, operation on the left hip for tuberculous osteomyelitis; (2) at 14 years, appendectomy for ruptured appendix; (3) at 15 years, laparotomy, thought by the patient to have been performed for tuberculosis; (4) at 20 years, laparotomy for intestinal obstruction; (5) at 27 years, nephrostomy; (6) at 28 years, laparotomy with bilateral salpingo-oophorectomy.

Beginning in 1938, she experienced repeated attacks of constipation; relief was obtained from cathartics. On Feb. 3, 1940 she entered the Baltimore City Hospitals with acute intestinal obstruction, which was partially relieved by conservative treatment. Later operation revealed numerous dense adhesions which were extensively divided. Her postoperative course was satisfactory, and she was discharged on the seventeenth postoperative day.

She was readmitted to the hospital on August 9, with recurrent intestinal obstruction. After a period of conservative treatment, laparotomy was again performed on August 23. The entire gastrointestinal tract was involved in dense adhesions. These were completely separated from the level of the stomach to the pelvic diaphragm.

At the close of the operation a Carrel tube with multiple openings in its central portion was inserted into the peritoneal cavity with ends projecting from the upper and lower angles of the wound. Before the patient left the operating room, 15,000 units of heparin in 500 cc. of physiologic solution of sodium chloride was injected through the tube into the peritoneum.

Twenty-four hours after operation the patient went into shock and for two days had a stormy postoperative course, the cause of which was not specifically determined. Laboratory studies during the first postoperative day showed a highest blood coagulation time of three and one-half minutes, a hemoglobin content of 105 per cent and a red blood cell count of 4,500,000. No more heparin was given.

After recovery from shock, the patient followed a satisfactory course for a period of six days; after this she became febrile. Two and one-half weeks later, a pelvic abscess was drained by posterior colpotomy. At this time she had also an infected abdominal wound, which was draining when she was discharged on October 13. This area was reopened when she returned to the hospital on October 29. She was discharged on December 20, and on March 11, 1941 she still presented a small sinus. There were no complaints of intraperitoneal origin.

This is definitely the type of case in which the use of heparin is indicated. It is necessary to point out, however, that in this instance neither the Connaught heparin nor liquaemin was employed. A domestic product was used which has given unfavorable reactions in laboratory experimentation. In view of the evidence of blood concentration during the first postoperative day, it is not believed that the unfavorable reaction was due to hemorrhage.

CASE 10.—A white woman 60 years of age was operated on by Dr. Cecil F. Freed at the Reading Hospital, Reading, Pa., on Dec. 14, 1940. She had undergone nine previous operations, mostly for repeated attacks of intestinal obstruction due to adhesions. Dr. Freed had performed two additional operations which required extensive separation of adhesions.

At a third operation, heparin was employed according to the standard technic with the exception of the use of two Pezzar catheters, one on each side of the

abdominal incision. The patient had an entirely smooth postoperative course and about one month later was free of symptoms.

CASE 11.—An adult woman was operated on by Dr. Cecil F. Freed at the Reading Hospital on Dec. 14, 1940. This patient had undergone cholecystectomy one year previously and was admitted to the Reading Hospital with pain and vomiting. After separation of the adhesions, heparin was used according to the standard technic. Her postoperative course was entirely smooth.

CASE 12.—L. M., a white woman 42 years of age, was operated on at St. Elizabeth's Hospital, Richmond, Va., by Dr. Guy W. Horsley on April 10, 1941. In 1935 the patient had undergone excision of the left ovary and resection of a portion of the ileum for endometriosis. In April 1940 she was operated on for intestinal obstruction due to volvulus. Twenty-eight centimeters of the ileum was resected. On admission in April 1941, a diagnosis of intestinal obstruction was made and immediate operation carried out.

An adhesive band from the mesentery to the cecum obstructing the small bowel and several other string adhesions were divided. Ten thousand units of heparin in 100 cc. of physiologic solution of sodium chloride was injected into the peritoneal cavity before closure of the wound. No more heparin was used. The patient had an entirely smooth convalescence without evidence of intraperitoneal hemorrhage and was discharged on the twenty-first postoperative day.

CASE 13.—W. E. H., a white woman 46 years of age, was operated on at St. Elizabeth's Hospital by Dr. J. Shelton Horsley on May 15, 1941. In 1932 she had undergone bilateral salpingectomy and excision of the right ovary elsewhere. After these procedures a painful ventral hernia developed. At a recent operation multiple peritoneal adhesions were separated; the right ovary was removed, and the hernia was repaired. A small catheter was passed through a stab wound in the right flank. Ten thousand units of heparin was injected into the abdominal cavity through the catheter one hour after operation, and 5,000 units was given in 500 cc. of physiologic solution of sodium chloride at twelve hour intervals for four doses; the total administration of heparin was 30,000 units. There were no evidences of intraperitoneal hemorrhage, and the postoperative course was entirely smooth. After the last injection, the patient complained of considerable abdominal pain.

This is the only case of discomfort as a result of postoperative instillation of heparin which has been reported to us. In our own experience the procedure has been entirely painless.

CASE 14.—V. B., a white woman 32 years of age, was operated on at St. Elizabeth's Hospital by Dr. Guy W. Horsley on July 8, 1941. Two years before she had undergone an operation elsewhere for a chocolate cyst of the right ovary. The symptoms suggested recurrence. At operation numerous adhesions were observed. The most important of these adhesions had drawn the cecum over the upper surface of the broad ligament. All adhesions were divided, and the raw surfaces peritonealized as far as possible. Five thousand units of heparin (liquaemin, Hoffmann-Laroche) were given once daily for three days through an inlying catheter. The patient had an entirely smooth recovery.

COMMENT

In 11 of the 14 cases of intraperitoneal heparinization herein reported (table) there was no evident effect on the postoperative course from

the administration of the drug except a transient elevation of the blood coagulation time (chart). The actual effect of the procedure on the reformation of divided adhesions is not known in any case. In 1 case there was a severe reaction to heparin of a brand now known to be toxic; in this case there was no evidence of bleeding, and recovery ensued. One patient died of intraperitoneal hemorrhage. In 1 case hemorrhage was suspected but not demonstrated; administration of

Data on Fourteen Cases in Which Intraperitoneal Adhesions Were Treated with Heparin

Case; Race	Sex and Age	Hospital or Surgeon	Previous Laparotomies	Previous Attacks of Obstruction	Heparin Product Used	Technic of Treatment	Postoperative Course
1 Negro	M 44	University of Virginia	0	0	Connaught	Modified	Slight ileus
2 Negro	M 34	University of Virginia	2	1	Connaught	Standard	Smooth
3 Negro	F 51	University of Virginia	1	0	Connaught	Standard	Smooth
4 White	M 53	University of Virginia	1	1	Connaught	Standard	Smooth *
5 White	M 60	University of Virginia	2	1	Connaught	Standard	Smooth
6 Negro	F 34	University of Virginia	2	1	Connaught	Standard	Died from hemorrhage (see text)
7 Negro	M 65	University of Virginia	1	1	Connaught	Modified	Symptoms suggested hemorrhage
8 White	F 40	F. M. Firor	Numerous	Several	Connaught	Modified	Smooth (slight wound hemorrhage)
9 White	F 45	J. C. Owings	4	2	Toxic brand	Modified	Severe toxic (?) reaction
10 White	F 60	C. F. Freed	11	Numerous	Connaught	Standard	Smooth
11 White	F Adult	C. F. Freed	1	?	Connaught	Standard	Smooth
12 White	F 42	G. W. Horsley	2	1	Connaught	Modified	Smooth
13 White	F 46	J. S. Horsley	1	?	Connaught	Modified	Smooth
14 White	F 32	G. W. Horsley	1	?	Liquaemin	Modified	Smooth

* Patient had a brief attack of bronchopneumonia and a superficial wound infection.

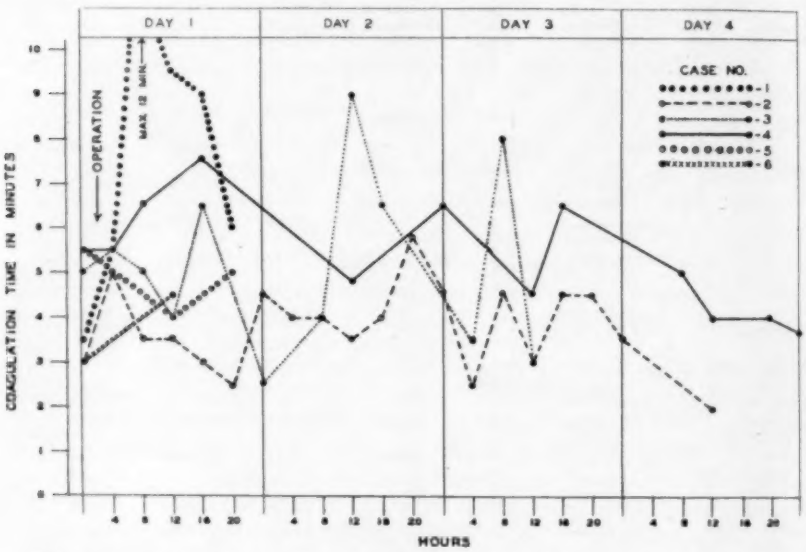
heparin was discontinued, transfusions were given, and the patient recovered.

In 11 of the cases there were no other complications worthy of note. There was apparently no greater incidence or degree of ileus than would ordinarily occur in a corresponding group of cases of obstruction treated without heparin. In 2 cases there were minor abnormalities in the healing of the wound. There was no apparent increase in average postoperative temperature readings and pulse rates. Postoperative discomfort was not increased.

As already stated, the single death can be blamed directly on poor judgment in selecting the case and on inadequate postoperative obser-

vation. If a tragedy in the use of this new method was destined to occur, it is fortunate that it occurred at the University of Virginia Hospital, where laboratory appraisal of the danger had already been made, and it is doubly fortunate that it occurred before the method was presented for clinical use. We have learned two lessons from this death.

The first and more obvious lesson is that care must be exercised to use heparin only in an unequivocally dry abdomen in which there has been no great difficulty in controlling oozing. This criterion will automatically exclude cases of recent laparotomy (such as case 6) in which granulation tissue is present.



Blood coagulation times after intraperitoneal heparinization in 6 cases of the University of Virginia Hospital series.

The second lesson is that no relaxation of vigilance in postoperative observation is permissible. Hemorrhage will remain the real hazard of the method; and possible hemorrhage must be foreseen in every case. This means that no matter what happy experiences may be had by the surgeons of any institution in 50 or 100 cases of intraperitoneal heparinization, those surgeons must not fail to follow the postoperative course of the next case with the same scrupulous care as they used in the first.

If these precautions are observed, we believe that the method is relatively safe for the type of patient who definitely needs protection from possible future intestinal obstruction. Until the actual effectiveness of the method in the human being is known, this opinion cannot be more than tentative. If definite benefit can later be shown in a large number of cases by a reduction in the number of intraperitoneal adhe-

sions, which would clearly diminish the chance of obstruction, then the choice between the risk of hemorrhage and the risk of later obstruction can be made on a firmer basis. Hemorrhage may, of course, occur in some cases, but there is slight reason that such hemorrhage need be fatal if detected early and treated adequately.

In the meantime, the method is proposed for clinical use in an entirely experimental and tentative way. We are planning to continue its use in the University of Virginia Hospital as long as properly selected patients, properly treated, continue to present uncomplicated postoperative courses.

In the presentation of a potentially dangerous method of treatment it is felt that a clearinghouse of information in regard to its application is important. We should therefore be grateful for immediate notification of any untoward experiences and for an occasional brief summary of successful use. We plan no further reports of cases from other clinics.

One warning, hardly necessary for experienced surgeons, must be issued. The object of an operation for acute intestinal obstruction is the cure of the acute attack. It is sound surgical treatment to combine no other intra-abdominal procedure, even an appendectomy, with the release of an offending band or bands. The surgeon must not yield to the temptation to add the burden of extensive separation of nonoffending adhesions in the sick patient because a possibly effective method of preventing future obstruction is at hand. If distention can be relieved by conservative measures, the possibility of widespread division of adhesions is increased. If distention cannot be relieved by conservative measures, it may be better in some cases to divide the obstructing band and to advise operation several weeks later for interval division of adhesions and heparinization. In cases in which there have been repeated attacks of obstruction, it may be sound not to wait for a fresh attack.

SUMMARY AND CONCLUSIONS

The indications, contraindications and technic of intraperitoneal heparinization in the human being for the prevention of the reformation of adhesions are presented and 14 cases are reported. In these cases there was one death. The single death was due to bad selection of the case and inadequate hospital observation.

Hemorrhage will remain a potential hazard in the application of the method described.

The method should not be applied if oozing is difficult to control or if there is granulation tissue present. Postoperative observation must be careful and continuous. With these precautions, the method is believed sufficiently safe to warrant further clinical trial.

No data on the effectiveness of the method in preventing adhesions in the human being are presented.

MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO SOFT TISSUE METASTASIS

J. LEWI DONHAUSER, M.D.
AND
WILLIAM H. DE ROUVILLE, M.D.
ALBANY, N. Y.

In 1928, Ewing [1] defined multiple myeloma as

> . . . a specific malignant tumor of the bone marrow arising probably from a single cell-type and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastases, albumosuria and fatal termination.

Vance,[2] considering the disease more from the clinical than from the pathologic standpoint, described multiple myeloma as characterized by

> . . . multiple primary tumors of the bone marrow, occurring, for the most part, in elderly individuals, and manifested during life by deep-seated pain in the bones, characteristic deformities of the skeleton, spontaneous fractures in many bones of the body, severe secondary anemia, and emaciation.

Geschickter and Copeland [3] emphasized that the

> . . . disease not only produces extensive involvement of the skeleton, but the systemic manifestations are particularly widespread and that changes in the central nervous system, the thorax, the lungs, the kidneys and in the blood picture are frequently prominent features.

These authors further stated that "a careful pathologic study shows that all of these various phases in the symptomatology and physical findings are secondary to the lesions originating in the bones."

Others look on the disease as being a systemic anomaly of the hemopoietic apparatus rather than a true tumor and as having a definite relation to leukemia and aleukemia.[4]

Slavens [5] defined the disease as

> . . . a primary malignant tumor of bone marrow characterized by multiple foci in long and flat bones of the skeleton and usually associated with anemia, Bence Jones proteinuria, rare metastasis and a fatal termination.

From the Department of Surgery of Albany Hospital and Albany Medical College.

1. Ewing, J., cited by Jackson, Parker and Bethea.[41]
2. Vance, B. M.: Am. J. M. Sc. **152**:711-712 (Nov.) 1916.
3. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, revised ed., New York, American Journal of Cancer, 1936, pp. 441-488.
4. Barker, L. F.: M. Clin. North America **16**:1019-1027 (March) 1933.
5. Slavens, J. J.: Multiple Myeloma in Child, Am. J. Dis. Child. **47**:821-835 (April) 1934.

Historically, five names are constantly associated with this disease: Bence Jones, Watson, McIntyre, von Rustizky and Kahler. Credit must be given also to Dalrymple, who gave the first microscopic description of this condition, which he had observed in two affected ribs.

On April 22, 1847, Henry Bence Jones[6] read the following words to his confrères of the Royal Society of London:

> On the first of November, 1845, I received from Doctor Watson the following note, with a test tube containing a thick, yellow, semi-solid substance: The tube contains urine of very high specific gravity; when boiled it becomes highly opake; on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but as it cools, assumes the consistence and appearance which you see: heat reliquefies it. What is it?

A few hours afterward, a specimen of the same patient's urine was sent to Bence Jones by McIntyre, who had been in attendance with Watson. McIntyre apparently noted the same phenomena as Watson. This was the beginning of the recognition of Bence Jones protein bodies as an occasional accompaniment of the then so-called mollities ossium.

Bence Jones began to make extensive studies and to set up hypothetic conclusions about the relation between the presence of these bodies and the disease mollities ossium. One of his conclusions was as follows: "So far as the albumin is concerned, each ounce of urine passed was equivalent to an ounce of blood lost."

Subsequently, McIntyre reported the first case of multiple myeloma to be recorded in the literature.

The term "myeloma" was introduced in 1873 by von Rustizky, who recognized the condition as a special disease of the bone marrow although in his case Bence Jones protein was not present in the urine.

In 1889, Kahler gave an excellent description of the disease, including as one of the characteristics the excretion of Bence Jones protein. However, it was not until 1897 and 1898 that Bozzolo in Italy awakened interest in this disease, and contributions including case histories of the disease soon followed.[7]

It was not until 1928 that Geschickter and Copeland[8] analyzed a series of 425 cases including those cited in the literature since 1845 and 13 cases of their own. The authors cited Martiri and Wallgren as contributing views on the subject (1915 and 1920, respectively).

CAUSATION

The disease is essentially one that occurs in the sixth decade of life with, according to Geschickter and Copeland,[8] the peak of incidence

6. Jones, H. B.: Phil. Tr. Roy. Soc. London **138**:55-62, 1848.

7. Bell, E. T.: Am. J. Path. **9**:393-415 (July) 1933.

8. Geschickter, C. F., and Copeland, M. M.: Multiple Myeloma, Arch. Surg. **16**:807-867 (April) 1928.

at 55. Its occurrence in children has been reported, but in most of the instances the diagnosis was not supported by microscopic examination. Berkheiser,[9] however, in his discussion of multiple myeloma in children, stated that the disease occurs in this age group as well as in adults.

Slavens reported a case in which the patient was a child 4 years of age with the "characteristic findings and involvement of the spleen, liver and aortic lymph nodes," though "repeated urinalyses gave negative results except for a trace of albumin on several occasions." This case occurred at the Mayo Clinic in 1934.

Geschickter and Copeland [8] mentioned trauma as present in 20 per cent of the cases; Oftedal [10] expressed the belief that it plays an important role but that "it is often of such a trivial nature as scarcely to be noticed by the patient at the time of its occurrence."

Family history and infection are not considered as causative factors.

Geschickter and Copeland [8] summed it up well when they stated:

> . . . All in all, the etiologic obscurity that is attached to malignancy seems to extend in no less degree to multiple myeloma.

After exhaustive studies, Geschickter and Copeland [8] came to the conclusion that multiple myeloma constitutes 0.03 per cent of all malignant growths. In 1918, Symmers [11] found only 3 cases in 4,000 postmortem examinations at Bellevue Hospital. In 9,000 autopsies at the Johns Hopkins Hospital there were 4 cases, and in 400 cases of sarcoma of the bone at Johns Hopkins Hospital, multiple myeloma was present in only 3 per cent.

CHEMICAL FINDINGS

The following data represent the blood chemical findings in normal persons.

Serum albumin, 4.6 to 6.7 per cent [12]
Globulin, 1.2 to 2.3 per cent [12]
Total protein, 6.5 to 8.2 per cent [12]
Calcium, 9 to 11 mg. per hundred cubic centimeters
Phosphorus, 3.7 mg. per hundred cubic centimeters
Sugar, 100 mg. per hundred cubic centimeters
Creatinine, 1 to 2 mg. per hundred cubic centimeters
Uric acid, 2 to 4 mg. per hundred cubic centimeters
Urea, 12 to 15 mg. per hundred cubic centimeters
Total nonprotein nitrogen, 25 to 30 mg. per hundred cubic centimeters

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9. Berkheiser, E. J.: Multiple Myelomas of Children, Arch. Surg. **8**:853-881 (May) 1924.

10. Oftedal, S.: Multiple Myeloma, J. A. M. A. **77**:1547-1548 (Nov. 12) 1921.

11. Symmers, D.: Ann. Surg. **67**:687-697 (June) 1918.

12. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med. **18**:455-473 (Oct.) 1916.

Phosphatase, 2.6 units per hundred milligrams with a wider increase of range in children.[13]

For many years calculations of serum calcium and of serum phosphorus have been made in diagnosing disease of bone because it has been known that in various disease conditions of the bones these determinations are affected. There is now a third determination, which is of the utmost importance, that of the serum phosphatase.

Mitchell and Crawford [13] and Simmons [14] have emphasized the importance of making a determination of this enzyme when diseases of bone are suspected, and Mitchel and Crawford add that

> . . . sufficient evidence has been produced in the past few years to establish the importance of serum phosphatase in the differential diagnosis and prognosis of several bone diseases.

After reviewing the phosphatase determination in several hundred cases, these investigators have shown that in patients with Paget's disease, the serum phosphatase may rise to twenty or more times normal and that in patients with the osteoblastic types of osteogenic sarcoma, in those with metastatic carcinoma of the bone and especially in those with hyperparathyroidism the serum phosphatase is elevated but that in those with multiple myeloma it shows no increase.

Robison [15] demonstrated that phosphatase, an enzyme extracted from bone and ossifying cartilage and from other tissues in smaller quantities, can liberate inorganic phosphorus by breaking down solutions of complex organic compounds of phosphorus, such as the glycerophosphates and the hexosephosphates. It is Robison's hypothesis that the phosphatase available in the cells of bone and ossifying cartilage reacts with the glycerophosphates or the hexosephosphatase in the blood. By this means there is produced a local increase of inorganic phosphorus in the region of these cells. This increase of phosphorus alters the calcium-phosphorus equilibrium, and calcium phosphate is deposited. That the enzyme is present in bone and in the circulatory system was shown by Martland, Hansman and Robison [16] and Roberts.[17] The presence in the blood of the type of organic phosphorus compound that may be broken down by phosphatase was demonstrated by Kay and Robison in 1924.[18]

13. Mitchell, C. L., and Crawford, R. G.: J. Bone & Joint Surg. **19**:630-637 (July) 1937.

14. Simmons, C. C.: Ann. Surg. **102**:555-562 (Oct.) 1935.

15. Robison, R., and Soames, K. M.: Biochem. J. **18**:740-754, 1924.

16. Martland, M.; Hansman, F. S., and Robison, R.: Biochem. J. **18**:1152-1160, 1924.

17. Roberts, W. M.: Brit. J. Exper. Path. **11**:90-95 (April) 1930.

18. Kay, H. D., and Robison, R.: Biochem. J. **18**:755-764, 1924.

It has been shown by these and many other investigators that in any disease in which there is concomitant formation of large amounts of new or abnormal bone there will as a rule be an elevation in the serum phosphatase. They have pointed out that the determination of this enzyme can be of value in both the diagnosis and the prognosis in cases of bone tumor, osteitis fibrosa cystica, Paget's disease and other conditions involving bone.

However, it should be borne in mind that there is likewise a variation in the serum phosphatase activity of patients having jaundice or nephritis or receiving a high carbohydrate diet.[18]

Kay [19] noted an increase in the plasma phosphatase of patients with osteitis fibrosa, osteitis deformans, active rickets and osteomalacia.

TABLE 1.—*Serum Calcium and Inorganic Phosphorus and Plasma Phosphatase in Various Conditions of the Bones (After Morris and Peden [21])*

Disease	Serum Calcium	Serum Phosphorus	Plasma Phosphatase
Osteitis deformans (Paget's)	N	N	++++
Generalized osteitis fibrocystica (Recklinghausen's)	++	—	+++
Solitary bone cysts (single or multiple)	N	N	N or +
Myeloma	N or +	N or +	N
Metastatic bone cancer	+	+	++
Osteogenic sarcoma	+	+	++
Other bone tumors	N	N	N
Rickets	N or —	—	++
Osteomalacia	N or —	—	++
Osteogenesis imperfecta	N	N	N or +
Senile osteoporosis	N or —	N	N

Bodansky and Jaffe [20] emphasized that a marked rise of plasma phosphatase does not necessarily accompany destruction of bone unless there is also present the formation of new bone or of osteoid tissue. In other words, the phosphatase is highest in cases in which there is excessive formation of abnormal osseous tissue. Morris and Peden [21] recently conducted investigations of the significance of phosphatase findings in the diagnosis of various diseases. Their table on differential diagnosis is included in this paper as table 1.

The absence of chemical changes in the blood in cases of multiple myeloma is, as a rule, so outstanding compared with the changes in cases of other anomalies otherwise presenting many of the same symptoms that chemical examination must be considered of great importance in the differentiation of this disease from others. However, occasionally there

19. Kay, H. D.: J. Biol. Chem. **89**:235-247 (Nov.) 1930.

20. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: Serum Phosphatase in Diseases of Bone; Interpretation and Significance, Arch. Int. Med. **54**:88-110 (July) 1934.

21. Morris, N., and Peden, O. D.: Quart. J. Med. **6**:211-230 (April) 1937.

is an increase in the globulin fraction in cases of this disease, and often there is an inversion of the globulin rates, but as Peters and Eisenman [22] stated:

> . . . Increases of globulin are found with infections, especially suppurative processes and ulcerative tuberculosis or syphilis; in connection with certain tumors, particularly myelomata; and in cirrhosis of the liver.

Cantarow [23] noted that at times there may be definite hypercalcemia in cases of multiple myeloma; this is demonstrated in a case in our series. However, hypercalcemia is not pathognomonic of the disease.

Hyperproteinemia is sometimes one of the most striking concomitants of this disease. The first case of true hyperproteinemia associated with multiple myeloma was reported by Perlzweig, Delrue and Geschickter.[24] Since that time reports of other cases have followed in rapid succession, and Sweigert [25] made the statement that the most striking examples of hyperproteinemia have been observed in cases of multiple myeloma, though reports of cases have been found in the literature of certain types of infection, notably kala-azar, of large tumors of the kidney and of other neoplasms in the diagnosis of which this symptom is of great importance. It must be remembered, however, that this symptom may not be present and that the total protein may be only slightly increased. As a general rule, however, hyperproteinemia should always be regarded with suspicion when it is present.

In 1933 Wintrobe and Buell [26] stated that in the reports of approximately 500 cases of multiple myeloma "abnormality in the blood plasma has been found only in 8 instances." They cited a case of their own in which hyperproteinemia was associated with multiple myeloma.

Reimann [27] reported a case of spontaneous rouleau formation of the red cells, which led to the discovery of marked hyperproteinemia. Foord [28] presented 4 cases of multiple myeloma in which there was profound autohemagglutination of the red cells and marked hyperproteinemia. In 2 of his cases there was uncontrollable prolongation

22. Peters, J. D., and Eisenman, A. J.: Am. J. M. Sc. **186**:808-833 (Dec.) 1933.

23. Cantarow, A.: Am. J. M. Sc. **189**:425-428 (March) 1935.

24. Perlzweig, W. A.; Delrue, G., and Geschickter, C. F.: Hyperproteinemia Associated with Multiple Myelomas: Report of Unusual Case, J. A. M. A. **90**: 755-757 (March 10) 1928.

25. Sweigert, C. F.: Am. J. M. Sc. **190**:245-256 (Aug.) 1935.

26. Wintrobe, M. M., and Buell, M. V.: Bull. Johns Hopkins Hosp. **111**: 156-165 (Feb.) 1933.

27. Reimann, H. A.: Hyperproteinemia as Cause of Autohemoagglutination: Observations in Case of Myeloma, J. A. M. A. **99**:1411-1414 (Oct. 22) 1932.

28. Foord, A. G.: Ann. Int. Med. **8**:1071-1089 (March) 1935.

of both bleeding and clotting time and an increased calcium content with little change in the platelet count. He further stated that the pronounced rouleau formation observed in the smears of the blood of 2 of the patients led to the procedures which terminated in making the final diagnosis of multiple myeloma. Schumacher, Williams and Coltrin [29] recently reported a case of plasma cell myeloma with an unusually high blood protein content, autohemagglutination, hemorrhage and renal insufficiency.

Hansen [30] reported 1 case in which there was hyperproteinemia due to an increase in pseudoglobulin. He assumed that functional disturbances in the cells of the bone marrow may be the underlying factor. He emphasized the fact that the Takata-Ora reaction may be positive in the disease, without apparent disturbances of the liver.

Decherd and Holland [31] recently mentioned 2 cases of multiple myeloma. In 1 there were hypercalcemia and hyperglobulinemia with a greatly accelerated sedimentation rate; Bence Jones protein was found in large amounts. In the second case there were retention of nitrogen in the blood without elevation of blood pressure and hypercalcemia with normal phosphorus content. The authors said "An increase in blood proteins is uncommon, and when found should lead to suspicion of multiple myeloma."

In 1938, Feller and Fowler [32] analyzed 52 cases of multiple myeloma with hyperproteinemia which they collected from the literature, and reported 3 of their own from a series of 10 cases of multiple myeloma.

Blood Viscosity: Albers [33] recently published his observations on the changes in the blood in 3 cases of multiple myeloma. He reported that in all 3 the viscosity was increased; in 2 the viscosity values surpassed "all hitherto observed values." In these 2 cases the globulin fraction of the serum was markedly increased; in the third case, which showed the least increase in viscosity, the globulin fraction was increased to only a minor degree. The viscosity did not decrease as the temperature increased but rather decreased "several times as much." This investigator attributes the increase in viscosity to the increase in the globulin content of the serum.

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29. Schumacher, I. C.; Williams, O. O., and Coltrin, G. S.: California & West. Med. **47**:174-177 (Sept.) 1937.

30. Hansen, O. S.: Multiple Myeloma, J. A. M. A. **79**:2059-2061 (Dec. 16) 1922.

31. Decherd, G. M., Jr., and Holland, L.: J. Trop. Med. **41**:129-132 (April 16) 1938.

32. Feller, A. E., and Fowler, W. M.: J. Lab. & Clin. Med. **23**:369-378 (Jan.) 1938.

33. Albers, D.: Ztschr. f. klin. Med. **132**:705-828, 1937; abstracted, J. A. M. A. **110**:407 (Jan. 29) 1938.

BENCE JONES PROTEIN

According to Anders and Boston,[34] Bence Jones protein is a normal constituent of the spermatic secretion and may be found in the bone marrow in cases of myeloma. According to most investigators, it is present in approximately 65 per cent of all cases of multiple myeloma. At times, frequent tests must be made of the urine before it is found, but its absence in no way excludes the possibility of the presence of the disease. This test is easily performed by any laboratory worker, and the detection of these bodies in the urine is of such extreme importance as a diagnostic factor in cases in which there is a suspicion of obscure myeloma that it should be carried out as a routine procedure whenever the disease is suspected.

Jacobson [35] reported finding Bence Jones protein in the circulating blood of a patient with multiple myeloma associated with advanced nephritis.

There are cases on record, and many of them, in which the finding of Bence Jones protein was the first clue to the existence of multiple myeloma. However, before stressing too much the import of Bence Jones protein, one must remember that this protein is often present with Hodgkin's disease, malignant tumor of the bone, especially diffuse carcinomatosis, lymphogranulomatosis, myxedema,[36] leukemia, cirrhosis of the liver and sometimes extensive suppurative processes. In fact, Bloodgood [37] reported a case in which Bence Jones protein was present in the urine of a patient with typhoid osteomyelitis of a rib.

Cantarow emphasized that frequently failure to detect Bence Jones protein is probably due to the fact that its characteristic properties of precipitation at relatively low temperaure and resolution at higher temperature are by no means invariably exhibited. He further stated that

> . . . the relatively rapid and marked fluctuations in serum protein and serum calcium concentrations in patients with multiple myeloma and the variability of the several factors which determine the characteristic precipitation reactions of Bence-Jones protein emphasize the necessity for repeated studies in such cases.

GROSS OBSERVATIONS

Myeloma involves most frequently and extensively those bones with the greatest content of red marrow. Thus the vertebrae, the ribs, the sternum, the clavicles and the skull are the most commonly affected, while the long bones, which are relatively cortical, are as a rule not

34. Anders, J. M., and Boston, L. N.: Lancet **1**:93-97 (Jan. 10) 1903.
35. Jacobson, V. C.: J. Urol. **1**:167-178 (April) 1917.
36. Caylor, H. D., and Nickel, A. C.: Ann. Surg. **97**:823-827 (June) 1933.
37. Bloodgood, J. C.: Progressive Med. **4**:229, 1906.

involved. Any of the bones, however, may become involved in the pathologic process. Grossly, the shell of bone embracing the tumor is of parchment thinness; it cuts readily with a knife. The tumor is extremely vascular and is made up of gray-red or dark red material; it is friable and of a more or less gelatinous consistency. The tumor is definitely destructive of bone.

Wells [38] remarked that a myelomatous growth may take on the characteristics of a neoplasm of vascular origin, retaining no remnants of the original tumor in the entire bony mass. He made the assertion, to which Ewing subscribed, that many a tumor described as vascular endothelioma of the bone and, sometimes, as a bone aneurysm, is really myeloma.

KIDNEYS

Perla and Hutner [39] concluded from their study of the pathologic changes in the kidney in cases of multiple myeloma associated with Bence Jones albumosuria that the following changes are present:

> . . . (1) a nephrosis specifically associated in some way with the Bence-Jones albumosuria and the myeloma; (2) arteriosclerosis of the kidney, an independent vascular disease of the kidneys, present in a milder or severer form in almost every instance . . . and (3) calcium deposits in the kidney tubules dependent on a destruction of bone and the release of large quantities of calcium in the blood.

Anatomically, the nephrosis is severe. Microscopically, the kidneys are contracted; there is extensive destruction of the tubules of the cortex and the medulla, with replacement by dense cellular fibrous tissue.

Perla and Hutner emphasized the importance of distinguishing the nephrosis of this disease from the idiopathic type. In multiple myeloma there are an absence of edema, an increase in the concentration of the nonprotein nitrogen in the serum and an inability to concentrate urine with a consequently low specific gravity of the urine.

Longcope [40] spoke of the occurrence in some instances of myeloid degeneration of the kidneys, the spleen and the liver.

James referred to the cells composing multiple myeloma as derived from the primary mesenchyma, *Wanderzellen*. He expressed the opinion that there is a definite relation between multiple myeloma and leukemia, aleukemia and other diseases of the lymphatic hemopoietic apparatus. Plasma cells are most prominent in the plasma cell type of multiple myeloma; in the myeloid type myeloblasts predominate. Extensive changes

38. Wells, H. G.: Relation of Multiple Vascular Tumors of Bone to Myeloma, Arch. Surg. **2**:435-442 (May) 1921.

39. Perla, D., and Hutner, L.: Am. J. Path. **6**:285-298 (May) 1930.

40. Longcope, W.: Internat. Clin. **2**:91-97 (June) 1927.

are occasionally present in the liver, the spleen and the kidneys, though their occurrence is far from constant.

In many cases studies of the kidneys show an entirely normal structure; in others in which there is associated Bence Jones protein, albumosuria, nephrosis, arteriosclerosis and calcium deposits are present. Anatomatically, nephrosis is severe; microscopically, there is extensive destruction of the tubules of the cortex and the medulla, with replacement by dense cellular fibroid tissue. Occasionally, pyelonephritis develops, resulting from compression of the spinal cord or from hypertrophy of the prostate.

Bell stated that the only direct effect of multiple myeloma on the kidneys is due to the formation of tubular casts of Bence Jones protein that obstruct and cause atrophy of the tubules. When large numbers of tubules are obstructed, extensive atrophy occurs, and renal insufficiency ensues.

Geschickter and Copeland [3] mentioned the fact that in recent years multiple myeloma, instead of being regarded as a true tumor, is considered by many as a disease of the blood-forming apparatus related to aleukemia and leukemia. Jackson, Parker and Bethea [41] use the terms "extraosseous" and "intraosseous plasmocytomata" but are hesitant to state whether true myeloma should be classed as an

> . . . intrinsic disease of the bone marrow or as a disease of the hemopoietic system in general, capable of involving extra-osseous structures and possibly even arising in them. According to Barr and Bulger,[42] who reviewed the writings of Beck and McCleary, of Ghon and Roman and of Piney, plasma cells have been demonstrated in the blood of patients with apparently typical multiple myeloma, and the spleen, the liver, the ribs, the sternum and the spine have been involved in cases of so-called plasma cell leukemia.

In 1936, Osgood and Hunter [43] reported a case of plasma cell leukemia. Patek and Castle [43] described another case and mentioned 11 previously reported. Reiter and Freeman [44] have summarized these cases as follows:

> A study of all possible cases reveals that the distinction between the localized form of the disease (plasma cell myeloma) and the diffuse form (plasma cell leukemia) is not a sharp one and any attempted classification such as that of Piney and Riach,[43] which considers the intermediate groups, must be arbitrary. We believe that all may be fundamentally a manifestation of the same process; nevertheless, it is obvious that some cases have certain outstanding characteristics acceptable as truly leukemic, which others lack.

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41. Jackson, H., Jr.; Parker, F., Jr., and Bethea, J. M.: Am. J. M. Sc. **181**: 169-180 (Feb.) 1931.

42. Barr, D. P., and Bulger, H. G.: Am. J. M. Sc. **179**:449-476 (April) 1930.

43. Cited by Reiter and Freeman.[44]

44. Reiter, B. R., and Freeman, J. T.: Am. J. M. Sc. **193**:38-42 (Jan.) 1937.

Jackson, Parker and Bethea classified the plasma cell type of multiple myeloma as malignant lymphoma; they concluded

> . . . that the disease in its classical form is largely limited to the bones does not militate against such a view when one considers the marked variation of the disease picture and the gradual manner in which the cases blend into each other.

Blatherwick [45] and Longcope found calcification in the liver, the spleen, the vessels of the heart, the lymph glands, the gastric mucosa and the kidneys; connective tissue was the main site of the deposits.

INVOLVEMENT OF THE SOFT TISSUES

In a monograph published seventeen years ago, Oftedal emphasized the importance of considering the multiple lesions found in the tissue as metastatic tumor rather than individual independent primary lesions of the blood-forming tissue, and he stated that "so far pulmonary metastasis has not been found."

Observers now more frequently record instances of involvement of the liver, the spleen, the lymph glands and the hemolymph glands, the cardiac muscle, the kidneys, the tonsils, the thyroids, the adrenal glands, the ovaries, the meninges and, less frequently, the pituitary gland, with tumor masses identical with those in the bone marrow.[46]

It is conceded that the blood-forming tissues are the favorite sites.

That tumor cells are found lying within the blood vessels, at times diffusely distributed in the sinuses of the liver and in the capillaries of the kidneys indicates metastasis rather than independent growth.

In 1934, Flax [47] stated

> . . . that while the individual tumors may be primary lesions, their distribution throughout the skeletal system lends all the clinical aspects of a widespread metastasis.

Wood and Lucké [48] reported large numbers of myeloma cells in the spleen and in the liver and expressed surprise that in view of the vascularity of the tumors and of the frequent presence of myeloma cells within the blood channels of the tumor these cells were not more often found in the circulating blood.

Gilmore [49] took a decided stand that multiple myeloma does not metastasize, although the "multiplicity of the lesions makes it appear to do so." He further stated that "pathologically, the disease does not

45. Blatherwick, N. R.: Am. J. M. Sc. **151**:432-436 (March) 1916.
46. Blackmar, M. L.: Personal communication to the authors, 1937.
47. Flax, N., cited by Graham,[69] 1934, pp. 97-98.
48. Wood, A. C., and Lucké, B.: Ann. Surg. **78**:14-25 (July) 1923.
49. Gilmore, M. E.: Texas State J. Med. **21**:358-362 (Oct.) 1925.

tend to extend locally" and that the "lesions remain confined to the bony system which is sorely damaged by the process."

In 1931, Jackson and Parker reported that in a series of cases of multiple myeloma

> . . . extra-osseous involvement occurred in 2 out of 17 classical cases, and in one of the plasmomata primary in a lymph node.

Willis [50] was not willing to commit himself as to whether lesions of myelomatosis are metastatic in nature or multicentric in origin.

Shennan [51] claimed that there are no true metastases of multiple myeloma. He said:

> The disease is confined to the osseous system, and may affect the greater part of it. Cases of apparent metastasis, such as Hoffmann's (in liver), Lubarsch's (in mediastinum), Verebély's (in larynx), and Kahler's (in inguinal region and in infra-spinatus), have to be submitted to careful scrutiny, seeing that such "metastases" are occasionally capable of another explanation than that they are true secondary colonies the formation of which characterizes malignant tumour-growth. Verebély's case is of special interest. In it an apparent metastasis had taken place to the cricoid cartilage, but this and other laryngeal cartilages had undergone ossification, with development of marrow. As for the other cases, it must be remembered that islets of haematopoietic bone marrow have not infrequently been demonstrated in soft tissues and organs outside the bones, and if multiple myeloma be regarded as a disease especially attacking functionating "red" marrow, then in that disease all such marrow, whether within or outside the bones, must be liable to undergo the peculiar transformation described.
>
> Still, even granting all this, we are not yet in a position either to affirm or deny that in rare cases myeloma may form true metastases in the soft tissues. The spleen, liver and lymph glands may become enlarged, congested, and beset with grey nodules and streaks, but these or similar changes occur in other diseases, and are not characteristic, and certainly not constantly remarked, in cases of multiple myeloma. As a matter of fact, when these organs show marked alterations in myeloma, an incorrect diagnosis may be suspected, or some intercurrent affection has obscured the issues. Nevertheless it must be recognized that competent observers have reported the presence in these organs of clusters of cells similar to those occurring in the local foci in the marrow.

Lubarsch [52] corrects an error of Saltykow [53] and Menne,[54] who published reports of 1 of his cases of myeloma; they claimed that two myelomatous nodules found in the soft tissues of the mediastinum represented metastases. According to Lubarsch, these nodules were in reality the result of direct extension from a focus in the marrow of the sternum with which they were connected.

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50. Willis, R. A.: The Spread of Tumors in the Human Body, London, J. & A. Churchill, 1934, p. 325.
51. Shennan, T.: Edinburgh M. J. **10**:321 and 414, 1913.
52. Lubarsch, O.: Virchows Arch. f. path. Anat. **184**:213-220, 1906.
53. Saltykow, S.: Virchows Arch. f. path. Anat. **173**:531-538, 1903.
54. Menne, E.: Virchows Arch. f. path. Anat. **183**:115-128, 1906.

He discussed also the various conceptions of myeloma and concluded that it is to be regarded not as true blastoma but as a systemic disease of the lymphatic-hemopoietic apparatus, closely related to leukemia.

He enumerated four forms: myeloma (myelocytoma), lymphocytoma, erythroblastoma and plasmacytoma. Multiple foci of involvement are explained by saying that the cells which are diseased are found in all these places in normal tissue, and hence the condition is not a primary tumor with multiple metastases but rather an outbreak of the disorder at various places in a single system. From this it follows that the soft tissues also may be involved, for plasma cells, myelocytes and erythroblasts are found in the soft tissues as well as in the bone marrow. The kidneys, the liver and the spleen are the soft tissues most often involved.

In reviewing the subject, Anders and Boston said, "Glandular enlargement is recorded in connexion with 15 per cent. of the cases, but in none of these did microscopic study show the growths of the glands to be identical with those developing from the bones."

Christian [55] gives a histologic comparison of 6 cases of myeloma. Of these, in only 1 was there involvement of the soft parts aside from direct extension. However, autopsy was not performed in all cases. In the case in question, in addition to multiple bone lesions, there was a nonsensitive movable tumor the size of an English walnut in the right axilla and two smaller masses on the right upper arm, apparently not attached to the bone. The microscopic description of the axillary node is as follows:

> In a section . . . there are numerous areas of epithelioid cells some of which contain also giant cells and form very typical tubercles. Besides this the sinuses here and there in the lymph nodes are filled with cells of the identical type of those previously described as occurring in the tumor. In places it is a question whether these masses of tumor cells are in true lymphatics, or growing as masses in the structure of the lymph node itself. However, the suggestion is that the tumor is pretty well confined to the lymph channels, while in the tissue about there are lymphoid and plasma cells of the ordinary type with the possibility of an occasional tumor cell, but this latter is open to doubt.

Christian cited a case of Hoffmann,

> . . . unique in that it is a characteristic myeloma with metastasis in the liver. Extension from bone to soft parts often occurs, but with the exception of Hoffmann's case and my Case III, metastasis is not reported.

Kaufmann [56] made the following statement:

> The question of metastases is much argued: it is closely related to the question of whether the myelomas are hyperplasias or true tumors, whether the latter may appear from the former, and whether these tumors are benign or malignant. Nodular myeloma formation occasionally occurs in other organs, such as the

55. Christian, H. A.: J. Exper. Med. **9**:325-351, 1907.

56. Kaufmann, E.: Pathology, translated by S. P. Reimann, P. Blakiston's Son & Co., 1929, vol. 2, p. 1217.

spleen, liver, kidneys, lymph nodes and others, and produces the picture of metastatic nodules. It is, however, probable, that these are not true metastases such as occur in malignant tumors, but merely an expression of a systemic disease of the hematopoietic apparatus.

A case was reported by Herrick and Hektoen,[57] the anatomic diagnosis in which was:

. . . Multiple tumors in the sternum, the ribs, the spine, the right clavicle, the left humerus, the right humerus, the left malar bone, the skull; invasion of the adjacent soft tissues and of the dura; tumors in the ovaries . . .

The ovaries were said to contain a few small tumors, of reddish color, firm in consistence and irregular in size and shape.

. . . Sections were made from most of the medullary tumors and from the growths in the ovaries. The structure is the same in all, and consists of round, lymphoid cells, with quite large nuclei arranged in a finely fibrillated, at times almost homogeneous matrix; in places they are very closely packed together, in other places more loosely. There are many blood-spaces of irregular size and shape found in the tumors, usually without any definite walls, the blood-mass being in direct relation with the surrounding wall of lymphomatous cells.

The authors mentioned also an article of Grawitz, describing

. . . a case of anemia following typhoid fever, in which round-celled sarcomatous tumors developed in the cranium, the vertebrae, the femora, the humeri, the bones of the legs, the right clavicle, the ribs, the sternum; there were also tumors in the liver, the right adrenal, and a disseminated involvement of the peritoneum.

Mention is also made of a case of Kahler's in which flattened, elevated masses appeared on the surfaces of the bones, particularly those of the ribs. At the end of six years there was marked kyphosis in the upper dorsal region of the spine and during the last year of life (the eighth year of the disease) the inguinal glands slowly enlarged. Microscopic examination revealed multiple development of a tissue with the characteristics of round cell sarcoma.

Horsch [58] recently noted that "tumors of the lymph nodes, spleen, or liver occasionally occur."

In our series of 5 cases, in all of which autopsy was performed, there was direct extension to the adjacent tissues in 1 case, the primary lesion being in the pubis (case 2). In case 3 there was definite metastasis to the myocardium, the retroperitoneum, the spleen, the liver, the adrenal glands, the ethmoidal sinus and the sella turcica. In case 4 there was definite metastasis to the lungs, the peritoneal lymph glands, the pancreas and the kidneys; in case 5 there was definite metastasis to the heart and to the spleen. (A description of the tissue will be given later.) In case 1 there was no evidence of either metastasis or extension.

57. Herrick, J. B., and Hektoen, L.: M. News **65**:239-242, 1894.

58. Horsch, K., abstracted in Graham, E. A.: Year Book of General Surgery, Chicago, The Year Book Publishers, Inc., 1935, p. 136.

To us these observations are of extreme importance. We feel that our 4 cases supply evidence to support the opinion that multiple myeloma may in many cases metastasize or extend by direct invasion of the surrounding tissue. It is interesting to note that in case 4 there was metastasis to the lungs.

SYMPTOMS

The possibility of multiple myeloma is to be considered in diagnosing the condition of a patient presenting headache, backache or pains of obscure origin in the bones, especially if the patient is a man in the sixth decade of life.[59] The pain is made more intense by motion or pressure and is subject to remissions and acute exacerbations. However, it may be intermittent, severe, wandering or recurrent and may be fugitive and not intense.[11] At times it may be quite bizarre and may be rheumatic in type.

The patient's attention may first be attracted to his illness by a sharp pain in the back or the thorax, brought on by sudden movement or muscular exertion. The attacks may be severe, the patient suffering for several days with "bone-breaking" pains in the lumbar and sacral regions or over the lower ribs. There may then be periods of intermittency and a so-called symptomatic period, which may last for several months. During the final stages of the disease, the pain reaches a climax, in which it attains its maximum intensity.

McConnell [60] first noticed severe precordial pains which radiated through the chest. Exertion made them worse, and they were followed by a sense of soreness felt all over but particularly through the abdominal and lumbar regions.

Spontaneous fractures are common and occur in about 62 per cent of all cases.[3] With probably no other disease of the bone, if we except osteogenesis imperfecta, are fractures so common.

It is not uncommon to find bronchitis and emphysema.

Blood pressure readings are of importance according to some eminent clinicians, such as Hammond,[61] who expressed the opinion that chronic nephritis with nonprotein nitrogen retention and a low blood pressure is typical of multiple myeloma. Other investigators have paid little attention to this finding, for Longcope, McConnell and others have described cases of their own in which the blood pressure has been as high as 190 systolic and 100 diastolic.

In 1937, Davison and Balser [62] reported 12 cases of multiple myeloma with special reference to neural complications. In the majority of their

59. Gros, W.: Deutsches Arch. f. klin. Med. **177**:461-474, 1935; abstracted, Arch. Path. **22**:562 (Oct.) 1936.

60. McConnell, G.: Am. J. M. Sc. **165**:184-195 (Feb.) 1923.

61. Cited by Geschickter and Copeland.[8]

62. Davison, C., and Balser, B. H.: Myeloma and Its Neural Complications, Arch. Surg. **35**:913-936 (Nov.) 1937.

cases in which lesions of the spinal cord were present the neurologic symptoms were produced by compression of the vessels of the spinal cord. They explained that a myelopathic process resulted from interference with the circulation. Herpes zoster was noted in a number of their cases; it was caused by direct compression of the spinal roots by the neoplasm.

It was interesting to note in this series of cases that in 1 case the myelomatous nodules of the cerebral dura and the skull interfered with the cerebral circulation and produced paranoic psychosis.

Of this series of 12 cases, in 6 of which autopsy was performed, there was involvement of the spinal cord, the spinal roots, the cerebral nerves or the brain. In 6 cases with signs of lesions of the spinal cord or the spinal roots, the neural structures were not removed.

There is such variation in the neurologic symptoms that we believe there is no definite symptom complex related to the peripheral or the central nervous system. Headaches, facial neuralgia and paraplegia, all may occur, depending on the involvement of the nerve roots and the stage of the disease.

Posture and deformities may play a most important part in the diagnosis. The patient often becomes shorter; the distance from the crest of the ilium to the shoulder is much reduced; the abdomen becomes protuberant; the chest becomes thick. In the anteroposterior plane, the patient may assume a most curious posture as he stoops. The knees are bent; the body is thrown in an abnormal position in order to keep balance; he bends over with difficulty and in so doing keeps his lumbar vertebrae fixed; he does not bend his spine.[40] Deformities may also occur from the presence of pathologic fractures.

Blood changes may show only anemia, though in most cases there is an increase in the lymphocytes, and the proportion of myelocytes often reaches 10 per cent.

PROGNOSIS

The average duration of life is two years,[3] though cases are on record in which the patient lived for only a few months after the inception of symptoms.[40] Anders and Boston stated that in cases in which albumosuria has persisted for some time its disappearance signifies approaching danger and probably an early death.

EXPERIMENTAL

As far back as 1906, Bloodgood suggested the possibility of extracting from the medullary tumors some specific serum for therapeutic purposes and felt that it should be tried.

With the premise that multiple myeloma might be a systemic disease of infectious origin, Harbitz [63] injected the tumor substance into animals; the results were negative in all cases.

Furth [64] showed that myeloid leukemia of mice can be readily transmitted to healthy mice by transfer of tissue which contains lime cells. He demonstrated that in almost every mouse in which resistance had been lowered by roentgen irradiation the inoculation was successful. He produced myeloid leukemia (a diffuse disease) in mice by intravenous inoculation of large doses and multiple myeloma (tumor formation) by subcutaneous or intraperitoneal inoculation.

At our suggestion, Dr. F. Byron, of the department of pathology of the Albany Hospital, carried out the inoculation of animals with tissue removed from the patient in case 1 of our series. On April 28, 1937, within one hour after the death of the patient bone marrow from the sternum was inoculated into laboratory animals at the sites indicated in table 2. The mice and the rats were killed three months

TABLE 2.—*Data on Inoculation of Plasma Cell Myeloma*

Animals	Species	Site of Inoculation
3	Mice	Subcutaneous
2	Mice	Intraperitoneal
2	Rats	Subcutaneous
2	Rats	Intraperitoneal
1	Hen	Subcutaneous
1	Hen	Intraperitoneal

after inoculation; there was no evidence of growth of the transplanted tissues at autopsy on August 6. The hens were kept for six months before being killed. No evidence of growth of the transplanted tissues was present at autopsy on November 2.

Ravdin and Morrison [65] reported that a "marked decrease in serum calcium after thyroparathyroidectomy retarded ossification, although it did not prevent union." In 1 case of our series there was hypercalcemia, and yet at autopsy no parathyroid tissue was found, even though the dissection was painstaking and the tissue which was subsequently removed as possibly containing the parathyroid glands was examined in serial sections. Bulger, Dixon, Barr and Schregardus,[66] finding a similar occurrence in a case in their series, hypothesized that the para-

63. Cited by Oftedal.[10]

64. Furth, J.: J. Exper. Med. **61**:423-445 (March) 1936.

65. Ravdin, I. S., and Morrison, M. E.: Ossification After Fracture: Experimental Study, Arch. Surg. **17**:813-828 (Nov.) 1928.

66. Bulger, H. A.; Dixon, H. H.; Barr, D. P., and Schregardus, O.: J. Clin. Investigation **9**:143-190 (Aug.) 1930.

thyroid gland plays a role in myelomatosis and other generalized bone diseases, as there is a similarity between these diseases on the basis of the disturbance of calcium balance that is common to them.

RELATION BETWEEN HYPERPLASIA OF PARATHYROID GLANDS AND MYELOMA

The fact that hyperplasia of the parathyroid glands may occur with myeloma has been cited as evidence that the latter disease is of parathyroid origin.[67] However, hyperplasia of the parathyroid glands has been observed also with metastatic carcinoma of bone, with rickets and with osteomalacia, and the majority of observers agree that hyperplasia of the parathyroid glands is undoubtedly a secondary, rather than a primary, factor in these conditions.

There are also reliable records of cases of multiple myeloma in which the calcium and phosphorus metabolism was normal and normal parathyroid glands were found at autopsy.

DIFFERENTIAL DIAGNOSIS

In reviewing the literature one is rather surprised to note the varied conditions which have been mistaken for multiple myeloma, and yet to the already long list we must add flatfoot. A diagnosis of flatfoot was first made and followed up therapeutically in 1 of the 5 cases reported in this paper. Neuritis, lumbago, rheumatism, chronic nephritis, chloroma, tumors of the spinal cord, renal rickets, metastatic carcinoma, metastatic hypernephroma, bone cysts, Pott's disease, Paget's disease, osteomalacia, osteogenesis imperfecta, Hodgkin's disease, generalized xanthomatosis, fibrocystic disease, all osteolytic bone lesions, enchondroma, basophilic adenoma, osteogenic sarcoma, endothelioma of Ewing and hyperparathyroidism have all at times been confused with multiple myeloma.

Owing to the rarity of multiple myeloma there is a "low index of suspicion" [25] among the physicians, especially when few cases seem to be alike and variations numerous. It is a disease which at times must be worked out by the pathologist, the chemist and the radiologist. The physician's part in the diagnosis is to suspect the condition and call for aid from the three aforementioned specialists. Even then a wrong interpretation of the roentgenograms, an error in diagnosis at biopsy and mistakes in chemical technic may well veil the identity of the condition for a variable length of time. One should be on guard, however, when-

67. Camp, J. D.: Roentgenologic Changes in Malacic Diseases of Bone, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1935, vol. 18, p. 1095.

ever an adult, especially a man, between the ages of 40 and 60, presents any or all of the following signs and symptoms:

1. Mild so-called rheumatic pain, at first perhaps generalized and impossible for the patient to locate definitely; the least contact may be dreaded; the pain is subject to acute exacerbations following a period of comfort for days, weeks, perhaps months; and yet there is no apparent invasion of the joints
2. Backache or severe thoracic pain
3. Spontaneous fracture
4. Progressing weakness and apparent anemia
5. The presence of a bony tumor mass, especially of the ribs, the sternum or the clavicle
6. Large amounts of albumin in the urine, with or without casts
7. Lumbar pain, with or without paraplegia
8. Continued low blood pressure with a nephritic syndrome
9. Shortening of stature

These clinical signs and symptoms, each and every one of them, should predicate the possibility of the existence of multiple myeloma or of one of the following conditions: (1) hyperparathyroidism, (2) metastatic carcinoma, (3) endothelioma of Ewing, (4) Paget's disease, (5) osteogenic sarcoma, (6) Hodgkin's disease, (7) lymphoblastoma (lymphosarcoma and leukemia), (8) neuroblastoma, (9) hypernephroma, (10) osteomalacia, (11) osteogenesis imperfecta, (12) osteopsathyrosis, (13) chloroma and (14) osteomyelitis.

A thorough physical examination may yield entirely negative results. If this happens, the situation demands investigation by the radiologist and the chemist just as promptly as though a tumor mass had been palpated or especial sites of tenderness had been located.

The radiologist should make roentgenograms of the skull, the ribs, the clavicle and a long bone, perhaps of the whole skeletal system.

The chemist should make complete and repeated examinations of the urine with special reference to the specific gravity, the presence or absence of albumin and sugar, the calcium content and most of all Bence Jones protein. Thorough and repeated examinations of the blood should be made, with estimations of calcium, phosphorus, phosphatase, total protein (including the albumin-globulin ratio), nonprotein nitrogen, creatinine, urea and uric acid. If either on clinical or on roentgen examination one finds a tumor mass, this should be surgically investigated and a specimen removed and submitted for microscopic examination. A biopsy will usually clinch the diagnosis. Physicians are urged to make postmortem examinations of the patients, for it is at the

autopsy table and in the pathologic and chemical laboratories that studies may give the clue to the cause of this at present incurable disease.

In no case of myeloma should the inoculation of fresh tissue into rats, mice, chickens and, perhaps, dogs and cats be neglected. So far inoculations have failed, but it is worth while to carry on in this particular line of work.

No observations are absolutely dependable, and there is no characteristic symptom complex. A biopsy is, of course, of paramount importance in reaching an absolute conclusion.

As Gilmore so well expressed it,

> . . . While the mistakes [in diagnosis] may not influence the course of the disease, the avoidance of them may obviate embarrassment to the practitioner, unnecessary treatment of the patient, and lead to an early, correct diagnosis. The lesions nearly always start in the vertebra and are diagnosed as Pott's disease. Multiple myeloma is seldom considered when back cases are being examined.

Hyperparathyroidism.—About hyperparathyroidism it is known that excessive parathyroid secretion causes a drain of lime salts from the body, resulting in skeletal changes, classified often as von Recklinghausen's disease or generalized osteitis fibrosa cystica. The disease usually begins between the ages of 15 and 35 years; it affects mostly women. Multiple myeloma, on the other hand, is essentially a disease of later life and affects mostly men.

The initial symptoms may be identical with those of multiple myeloma. Diffuse, so-called rheumatic pains with tenderness in the bones or the joints, progressive weakness, gradual loss of weight and early fatigue are commonly found in the early stages. As the disease progresses, spontaneous fracture may occur and indeed may be the first real sign of the condition, though a careful history will usually elicit one or more of the aforementioned symptoms as having existed before the fracture. Attacks of abdominal pain with nausea and vomiting, signs of secondary anemia and frequency of urination often bring the necessity of roentgen examination to the attention of the physician. The finding of a small tumor in the thyroid region may aid in the diagnosis, though this is so rarely detected clinically that nothing should be concluded from its absence. Nephrolithiasis may accompany this condition. A determination of the chemical composition of the blood in this disease is of paramount importance. There is a negative calcium and phosphorus balance, associated with hypercalcemia and hypophosphatemia. The phosphatase activity is marked. The similarity between myeloma and hyperparathyroidism appears occasionally to be on this basis of disturbed calcium balance, for it must be borne in mind that in many cases of multiple myeloma, the calcium level is elevated, although the phosphorus and phosphatase levels are usually normal or only slightly elevated. In cases of hyperparathyroidism, the urine and

feces contain abnormally large amounts of calcium; in cases of multiple myeloma, they do not. Bence Jones protein is practically never found in the urine in cases of hyperparathyroidism, though it is commonly detected in cases of multiple myeloma.

Roentgen findings are discussed in the section of this paper on roentgenographic differential diagnosis, page 968.

Metastatic Carcinoma.—There is frequently found the primary growth or the history of one having previously been discovered and operated on, such as carcinoma of the breast or of the prostate gland. Anemia, which is usually present, is accompanied by the clinical manifestations of anemia and progressive weakness. The roentgenologic observations are as a rule typical of the disease. Bence Jones protein is not present except in rare instances. Hyperproteinemia is rarely present. There is no inversion of the globulin ratio; usually, mild hypercalcemia and increase in the phosphorus content of the blood with an increase in the phosphatase become manifest. Ordinarily, the age is above 40. Fractures are fairly frequent, especially in the long bones.

Endothelioma of Ewing.—Endothelioma of Ewing regularly occurs in the first two decades of life, especially in men. Trauma is undoubtedly a predisposing factor; multiple skeletal involvement is rare. The shafts of the tibia and fibula are most often the sites of the disease, and the roentgenograms are characteristic. The presence of Bence Jones protein has never been reported with this disease, and the results of chemical analysis of the blood are usually negative, though there may be a slight increase in calcium and in phosphatase. Fractures occur only in rare instances. As the disease advances, secondary anemia may occur.

Paget's Disease.—Of itself Paget's disease is rarely confused with multiple myeloma, but it occasionally happens that malignant changes may so change the picture as to render intensive study necessary. Patients with this disease are over 45 years of age and mostly men. The square skull, the lateral bowing of the femurs and the tibias and the lordosis in patients with this disease readily suggest the diagnosis of this condition. The roentgen observations of marked new bone thickening, of a woolly appearance of the bones of the skull and of generalized skeletal involvement are quite pathognomonic. There is an absence of Bence Jones protein. Determinations of phosphatase show an enormous increase. The content of calcium in the urine is decreased.

Osteogenic Sarcoma.—Generalized skeletal involvement is extremely uncommon; constitutional signs are consistent with the blood picture of anemia. Fractures and the presence of Bence Jones protein are uncommon. There is an increase in the calcium and the phosphorus of the blood, and the phosphatase level is elevated. In a recent case of

ours, phosphatase was as high as 11.6 Bodansky units. The total protein may be high, though the ratio of globulin and albumin is within normal bounds. Roentgen findings are usually typical, and the lesion generally occurs primarily at the end of a long bone.

Osteomalacia.—Osteomalacia is rarely confused with multiple myeloma, and yet the multiplicity of the lesions, the frequency of fracture and the generalized osteoporosis may be mistaken for multiple myeloma. An analysis of the signs and symptoms of this disease should readily suggest the correct diagnosis. It is essentially a disease of women at the child-bearing age or at senility, though it must be remembered that it may occur in men. It is a slow and progressive osteoporosis most especially involving the thorax, the pelvis and the long bones. No Bence Jones protein is found. The blood calcium and phosphorus are decreased, while the phosphatase shows an increase, perhaps marked. Fractures are common. This disease has a well defined roentgen picture and is rarely associated with bone cysts.

Hodgkin's Disease.—Morrison [68] expressed the opinion that Hodgkin's disease is a loose diagnostic term for a number of hematogenic tumor growths. The osseous system is involved in from 10 to 50 per cent of the cases. Often there are no clinical signs, and the disease is found only by roentgenograms. In rare instances Hodgkin's disease may occur primarily in the bone.

Hodgkin's disease, lymphosarcoma, lymphoblastoma and leukemia will be discussed as a group with regard to the problem of differentiating them from myeloma. All sometimes give rise to generalized skeletal involvement, and the similarity of the signs and symptoms presented by this group of diseases is so marked that without biopsy it may be impossible to differentiate them. Although the age index is below that of myeloma, this group of diseases may affect patients up to the age of 60 or older. Vague pains in the bones and joints, abdominal discomfort, nausea and vomiting, loss of weight and strength, spontaneous fracture and even fever may be present in cases of this group of diseases as well as in cases of myeloma. The blood will show, at least in the later stages, the picture of secondary anemia, or in cases of leukemia, the typical picture of that disease. The occasional occurrence of eosinophilia with Hodgkin's disease may be a helpful aid to diagnosis. Glandular enlargement, so commonly present in cases of Hodgkin's disease, also helps. Roentgen examination is of great importance. See the section on roentgenographic differentiation, page 968. Bence Jones protein is seldom present in the urine in patients with this group of diseases; if it is, one should seriously consider the possibility of myeloma. Chemical examination of the blood may or may not be helpful. In cases

68. Morrison, M. C.: Canad. M. A. J. **34**:393-396 (April) 1936.

of Hodgkin's disease there is more likely to be an increase in the blood calcium, though there are many cases of myeloma in which hypercalcemia is present. An increase of phosphatase and a decrease in the phosphorus content of the blood is important. Seldom, if ever, is there a decrease of phosphorus in the blood of the patient with multiple myeloma, though there is sometimes a slight increase in the phosphatase.

Neuroblastoma of the Adrenal Glands.—Neuroblastoma of the adrenal glands is essentially a disease of infancy and early childhood. The first symptom may be bone pain; occasionally an enlarged bone is the first sign. Hematuria or perhaps secondary anemia may first bring the physician's attention to the possibility of the presence of this disease. A mass in the region of the kidneys usually confirms the diagnosis. See the section on roentgenographic differentiation that follows. As the lesion is of such a destructive nature, phosphatase may be increased.

ROENTGENOGRAPHIC DIFFERENTIATION

Myeloma.—In the interpretation of roentgenograms taken in cases of suspected myeloma, it must be understood "that in order to arrive at a correct opinion the Röntgen-ray must show in detail the structure of the bones examined and the plates must be read by a person who can detect abnormal difference in density even though slight." [48]

The most characteristic feature is the diminished density of the involved bones associated with absorption and replacement of lime salts by tumor tissue. The skull and the other bones usually show sharply punched-out holes. These holes may be extremely numerous. Within the tumor the absorption of bone is complete,[60] producing a rounded central area, which is sharply demarcated. In other words, no bone production is evident; there is no compensating hyperostosis. As the tumor grows, the periosteum and the epiphysis become invaded, and there gradually appears the diminished density mentioned.[52]

The lesion is usually central and multiple, though the tumor may appear as a solitary central mass, gradually destroying and absorbing the cortex in all directions.[60]

"It should be constantly borne in mind that bone resorption, which is practically always present, may be the key to the histogenesis." [69]

Flax said, "So far as is known, the neoplasm does not metastasize but remains locally destructive." Our cases and those of others tend to disprove this assertion.

It must be remembered, however, that there is nothing definitely characteristic about the multiple punched-out destructive lesions; therefore, other types of destructive bone lesions must always be taken into consideration. Fracture is extremely common.

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69. Graham, E. A.: Year Book of General Surgery, Chicago, The Year Book Publishers, Inc., 1932, p. 125.

Endothelioma of Ewing.—Endothelioma of Ewing is usually found in the midshaft region of a long bone, especially in that of the tibia or the fibula. There may be metastasis to any part of the skeletal system, the lungs, the lymph nodes and other soft tissues. There is involvement of a single bone early in the disease, with later dissemination to other bones. The tumor begins within the medullary canal and produces an infiltrating soft mass which erodes the cortex more or less extensively. It may break through widely and lift the periosteum, stimulating extensive formation of new bone. As a rule, the density of the bone is increased by its vigorous reaction to tumor invasion in the subperiosteal and endosteal regions. The shaft becomes expanded, and the cortex widens and becomes dense. The marrow cavity becomes mottled, and finally both cortical and medullary destruction appears. At first, the formation of bone predominates, giving rise to either parallel or radiating spicules. The tumor tissue itself possesses no properties of osteogenesis; the so-called onion cell formation is the result of multiple parallel rows of reactive bone being separated by tumor tissue. In some cases the extent of bone reaction is proportionately greater than the rapidity of tumor growth, resulting in a broad sclerotic shaft. There may be transverse striations, fine hairlike processes projecting at right angles from the periosteum. It must be remembered that this tumor has no great tendency to metastasize to any skeletal sites, but this may occur, as mentioned before.

Hyperparathyroidism.—Various stages of hyperparathyroidism present varied roentgen pictures. The most constant finding is a generalized reduction in the density of the vault of the skull, which is characterized by a fine, porous appearance with scattered areas of moderate thickening but with no dense areas of calcification; generalized skeletal involvement usually follows. Lacunar resorption with fibrosis of the bone marrow and the formation of osteoclastoma is noted roentgenographically. In about half, or a little over half, of all the cases, cysts are present too. General osteoporosis occurs, more pronounced in some areas than in others, but formation of bone does not cease. Pathologic fracture is common.

Metastatic Carcinoma.—Osteolytic metastases simulate most closely the lesions noted in cases of multiple myeloma. The former are usually less circumscribed, and large isolated lesions are common—an uncommon observation in cases of multiple myeloma. In cases of osteolytic metastasis a definite differential roentgen diagnosis may be impossible. The presence or operative history of primary carcinoma may establish the diagnosis.

Osteoplastic metastases are regularly more easily differentiated. These lesions are in close proximity to the nutrient arteries; they are

not so extensively distributed as multiple myeloma. Although the bone is infiltrated by the tumor, which produces absorption of bone, there is stimulating osteogenesis on the part of the local bone, and production of bone is present throughout the metastatic areas. The bone is thus strengthened, and although pathologic fracture occurs, it is far from common. Gross shortening of the spine, if the spine is involved, is less frequent than in cases of multiple myeloma, and unless there has been primary carcinoma of the cervix or carcinoma of the breast, the ribs are rarely involved, a condition frequently noted in cases of multiple myeloma.

Osteolytic or osteoclastic metastases have much the same distribution as plastic lesions, but they destroy bone by ossifying and stimulate little formation of surrounding new bone. The osteolytic type of metastatic carcinoma simulates multiple myeloma most closely. The former is ordinarily less circumscribed, and isolated lesions may be much larger. The presence or history of operative removal of primary carcinoma establishes the diagnosis.

Paget's Disease.—In cases of Paget's disease there is lacunar resorption, but apposition is more marked, and regional areas of dense ossification or calcification are common. The characteristic appearance of the skull is described as woolly. The bones of the calvarium are remarkably thickened and made up of areas of varying density, with an inner and outer table that is fuzzy. The tibias become bowed. Formation of cysts may occur beneath the cortex. The pelvic bones and the femurs when these are involved present similar characteristics. There is widening of bones by new bone of decreased density. Bone absorption is replaced by ossification of a low order. The bones become elongated and enlarged; added to this is the bending. Lytic changes in the medullary cavity are extremely rare, unless a malignant lesion accompanies the condition. There are smooth, expanded cortices, not the irregular margins of metastatic carcinoma.

REPORT OF CASES

CASE 1.—D. A., a 57 year old white farmer, was admitted to the Albany Hospital on March 24, 1936. His chief complaint was pain in the back, in the right side of the chest and in the shoulders.

History of Illness.—In June 1935, the patient was jacking up his automobile, when he felt a sudden catch in the left side of his chest. It was so painful that he could hardly straighten up. He applied adhesive strapping, but the pain became worse and radiated to his left shoulder and back. About ten days later he turned suddenly and felt a sharp snap in his back. It was several moments before he could straighten himself. At this time he had severe pain over his whole chest and dyspnea. He was treated by his family physician with heat, strapping, rest and colloidal sulfur. He was told that he had pleurisy.

In August 1935 roentgenograms were taken by a roentgenologist. The patient stated that he was not informed of the interpretation of the plates. He did little work after that. Whenever he exerted himself at all, he had severe, sharp pains in his chest, shoulders and back. He was seen by several physicians. He noted a gradual decrease in stature in the last few months before admission and was considerably shorter than formerly.

Past History.—Fifteen years before admission the patient fell from a tree and struck the middle of his back on a rock. After this he had pains similar to those present on admission, but less severe. In 1909, an appendectomy was performed. No other serious illness, accidents or operations had occurred.

A review of the systems showed them to be essentially normal.

Fig. 1 (case 1).—D. A., a 57 year old farmer, the patient in case 1; note the marked kyphosis.

Familial History.—His father had died of "prostate trouble" and his mother of "creeping paralysis." Otherwise the familial history was noncontributory.

Examination.—The patient was a well developed and well nourished man, 57 years old, who walked with a hesitant gait. His shoulders were stooped, and his body appeared foreshortened. There was marked kyphosis. He experienced no particular discomfort except for an occasional dull pain in the back and throughout the chest.

The head was normal. The pupils were equal and regular and reacted to light and in accommodation. The tongue was coated and protruded in the midline without tremor. The ears and nose were apparently normal. The pharynx was injected but otherwise apparently normal. Teeth were missing. The neck was normal and the glands not palpable. The pulmonary sounds were clear and resonant, and no rales were heard. Pain was elicited by pressure over the whole chest wall and was most severe in the lower part of the right side. The apex

beat was in its normal position. The heart was not enlarged; the sounds were regular, and no murmur was present. There was no adenopathy.

The blood pressure was 110 systolic and 70 diastolic. Through the abdomen the patient was obese. An old appendectomy scar was noted. There were no masses or tenderness in the abdomen, and there was apparently no inguinal glandular enlargement. The back was rigid, especially in the thoracic and lumbar region; there was fairly marked dorsal kyphosis, with pain on pressure over the lower thoracic vertebrae. Rectal examination revealed no abnormalities. The reflexes were normal.

The Wassermann test was negative.

The basal metabolic rate was 8 per cent.

The urine on the day after admission was normal. Bence-Jones protein was not found.

A complete examination of the blood (hemoglobin, red cell count, white cell count, differential count) yielded essentially negative results.

On the day after admission the blood calcium was 13 mg. per hundred cubic centimeters. Culture of the blood yielded no growth of bacteria.

A plaster of paris jacket was applied, and the patient was advised to return to the hospital within a few days for further hospitalization, biopsy of a rib and high voltage roentgen treatment.

The interpretation of roentgenograms by the hospital's roentgenologist favored the diagnosis of hyperparathyroidism. The patient left the hospital on March 28.

The patient was readmitted to the hospital on April 7. His condition was practically the same as it had been ten days previously. Since his discharge he had worn the plaster jacket and said he had received a fair amount of relief from it. He still had dull and continuous pain across the anterior wall of the chest and posteriorly between the shoulder blades; the pain became more acute when he moved about. He had no new complaints. There was no dyspnea and no cyanosis, and he did not appear acutely ill. Marked hyperalgesia was apparent on percussion over the lower part of both walls of the chest.

The blood pressure was 92 systolic and 68 diastolic.

On April 10, with the patient under anesthesia induced with nitrogen monoxide and ether, an incision approximately 8 cm. long was made in the area over the tenth rib on the right side, slightly anterior to the midaxillary line. In this area there was a definite neoplastic mass, semisolid in consistency and in places parchment-like to the touch. The rib was partially eroded, and the tumor had extended into the pleura beneath and toward the rib elbow. The tumor was composed of a soft reddish, hemorrhagic material. Approximately 5 cm. of the rib and surrounding tissue was removed. The microscopic diagnosis was plasma cell myeloma.

A phenolsulfonphthalein test on April 25 showed 25 per cent excreted during the first hour and 20 per cent during the second hour.

On April 12 a sedimentation test gave the following results:

Walton tube (normal, less than 6 minims [0.37 cc.] at the end of one hour)	16.5 minims
Volume of packed red blood cells (normal, 0.4-0.45 cc.)	0.4 cc.
Wintrobe method	0.26 mm. at the end of twenty minutes

The blood pressure readings, the blood counts, the complete results of the chemical examination of the blood and of the urine are given in tables, 3, 4, 5, 6 and 7. For the roentgen findings, see page 982.

TABLE 3.—*Blood Pressure Readings of the Patient in Case 1*

Date	Blood Pressure	Date	Blood Pressure
3/25/36	110/70	9/15/36	92/74
3/27/36	102/78	10/20/36	102/74
4/ 7/36	92/68	11/15/36	98/64
4/20/36	90/58	12/18/36	92/74
5/ 5/36	88/56	2/ 4/37	104/80
5/25/36	84/62	4/17/37	110/70
6/15/36	84/60	4/25/37	100/50
7/10/36	90/68	4/27/37	90/58
8/ 7/36	96/76		

TABLE 4.—*Blood Counts of the Patient in Case 1*

					Differential Count					
Date	Hemoglobin, per Cent	Red Blood Cell Count	Color Index	White Blood Cell Count	Polymorphonuclears	Eosinophils	Basophils	Lymphocytes	Myelocytes	Comment
3/24/36	95	4,650,000	1+	7,100	60	1	...	34	5	Normal
4/ 8/36	90	5,310,000	0.8	9,250	74.5	4	0.5	13.5	7.5	Normal; platelets, 225,000
4/13/36	90	6,380,000	0.7	8,200	64.5	1	0.5	31	3	Normal; many basket cells
4/16/36	87	5,690,000	0.7	6,300	76	2	0.5	15	6.5	Platelets increased
4/20/36	83	4,780,000	0.8	5,600	75	2	0	17.5	5.5	
4/23/36	83	4,070,000	1	4,700	76	1	0	20	3	
5/ 8/36	73	4,240,000	0.8	4,050	61	2	0	32	5	Normal
5/25/36	87	4,840,000	0.9	3,950	60	1	...	34	5	Normal
7/10/36	84	4,720,000	...	4,570	62	1	...	33	4	Platelets increased; many basket cells
7/26/36	79	3,830,000	...	6,300	65	2	1	29	3	Slight irregularity in the size of the red blood cells
8/ 7/36	72	3,510,000	1	7,280	61	2	1	29	7	Normal
10/20/36	77	4,010,000	...	4,800	63	1	0	32	4	Normal
11/15/36	70	3,900,000	...	4,200	60	2	1	32	5	Slight irregularity in the size of the red blood cells
2/ 4/37	75	3,720,000	...	5,100	61	1	0.5	34	3.5	No abnormal cells noted
4/17/37	80	3,800,000	1+	10,000	84	0	0	12	4	Mild achroma
4/20/37	77	3,620,000	1	8,800	82	0	0	13	5	Platelets, 430,600
4/25/37	75	3,500,000	1	8,000	80	0	0	14	6	Not remarkable

TABLE 5.—*Results of Chemical Analyses of the Blood of the Patient in Case 1*

Date	Calcium, Mg. per 100 Cc. (Normal, 9-11)	Phosphorus, Mg. per 100 Cc. (Normal, 3.7)	Phosphatase, Units per 100 Mg. (Normal, 2.6)	Nonprotein Nitrogen, Mg. per 100 Cc. (Normal, 25-30)	Creatinine, Mg. per 100 Cc. (Normal, 1-2)	Uric Acid, Mg. per 100 Cc. (Normal, 2-4)	Urea, Mg. per 100 Cc. (Normal, 12-15)	Dextrose, Mg. per 100 Cc. (Normal, 100)	Albumin, per Cent (Normal, 4.6-6.7)	Globulin, per Cent (Normal, 1.3-2.3)	Total Protein, per Cent (Normal, 6.5-8.2)	Albumin-Globulin Ratio	Carbon Dioxide Combining Power, per Cent	Congo Red Test, per Cent
3/25/36	13.0	...	...	....	....	....	....	....	...	...	...	...	..	..
3/27/36	12.4	...	...	....	....	....	....	....	...	...	...	...	..	..
3/28/36	13.4	..	...	....	....	....	....	....	...	...	...	...	..	..
4/ 8/36	14.2	3.6	Negative	36.8	1.31	2.14	10.4	86.6	...	...	...	...	..	..
4/19/37	12.6	4.0	3.6	60.0	1.52	2.10	29.6	126.6	5.1	4.1	9.2	1.2	..	..
4/26/37	9.7	2.8	3.4	....	....	1.70	19.5	....	4.6	2.8	7.4	1.6	..	..
4/27/37	....	...	...	31.0	1.20	....	....	74.0	...	...	...	...	..	..
4/20/37	....	...	...	....	....	....	....	....	...	...	...	...	..	44 removed
4/27/37	....	...	...	....	....	....	....	....	...	...	...	...	61	..

Treatment and Course.—While in the hospital the patient received a course of high voltage roentgen therapy. He was discharged on April 27. During the summer months he was seen frequently and repeated examinations of the blood, the urine and the blood pressure were made.

On August 7 the patient returned to the hospital for another course of high voltage roentgen therapy. He said that he had experienced considerable improvement since his last admission; his chief difficulties now were pain in the right shoulder, stiffness in the back of his neck and, at times, a sense of suffocation. He also noticed increased frequency of urination.

TABLE 6.—*Results of Examinations of the Urine of the Patient in Case 1*

Date	Reaction	Specific Gravity	Albumin	Sugar	Acetone	Diacetic Acid	Bile	Microscopic Observations	Bence Jones Protein
3/25/36 (1st admission)	Neutral	1.015	0	0	0	0	0	0	0
4/ 7/36 (2d admission)	Acid	1.015	..	0	0	0	0	Few white blood cells	+
4/ 8/36	Acid	1.011	0	0	0	0	0	Few granular casts	0 (a.m. and p.m.)
4/ 9/36	Acid	1.012	0	0	0	0	0	Granular casts; few white blood cells	+
4/10/36	.....	.....	..	..	..	..	..	.....	0
4/11/36	.....	.....	..	..	..	..	..	.....	0
4/12/36	.....	.....	..	..	..	..	..	.....	+
4/13/36	.....	.....	..	..	..	..	..	.....	+
4/14/36	.....	.....	..	..	..	..	..	.....	0
4/15/36	Acid	1.020	+	0	0	0	0	Rare granular cast; calcium oxalate	+
4/16/36	.....	.....	..	..	..	..	..	.....	0
4/17/36	.....	.....	..	..	..	..	..	.....	0
4/18/36	.....	.....	..	..	..	..	..	.....	0
4/22/36	Acid	1.020	0	0	0	0	0	0	
5/ 5/36	Neutral	1.012	Trace	0	0	0	0	Occasional white blood cell	0
5/ 8/36	Acid	1.010	0	0	0	0	0	Negative	0
5/19/36	Acid	1.022	0	0	0	0	0	Occasional granular cast	+
5/25/36	Acid	1.014	0	0	0	0	0	Granular casts	+
6/15/36	Acid	1.012	0	0	0	0	0	Occasional white blood cell	0
7/10/36	Acid	1.010	0	0	0	0	0	Negative	0
7/26/36	Acid	1.014	0	0	0	0	0	Granular casts	+
8/ 7/36	Alkaline	1.008	0	0	0	0	0	Few hyaline casts	
9/15/36	Acid	1.020	Trace	0	0	0	0	Negative	+
10/20/36	Acid	1.014	0	0	0	0	0	Negative	0
11/15/36	Acid	1.024	Trace	0	0	0	0	Occasional granular cast	+
12/ 8/36	Acid	1.020	0	0	0	0	0	Negative	0
2/ 4/37	Acid	1.004	Trace	0	0	0	0	Granular casts	+
4/17/37	Alkaline	1.000	4+	0	0	0	0	Negative	0
4/20/37	Acid	1.012	1+	0	0	0	0	Occasional granular cast	
4/21/37	Acid	1.014	Trace	0	0	0	0	White blood cell detritus	
4/24/37	Acid	1.010	Trace	0	0	0	0	White blood cells	0
4/25/37	Acid	1.012	Trace	0	0	0	0		
4/26/37	Acid	1.012	Trace	0	0	0	0		
4/27/37	.....	.....	..	..	..	..	..	.....	+

Although the patient's pain was better, it was noted that his breathing was more difficult and that the kyphosis had increased. Extension, lateral bending and rotation of the head were performed incompletely and with deliberation. Flexion was normal. The head was held slightly fixed in walking. The fourth and the fifth ribs were bilaterally prominent; the sternum was bulging, and the prominence and sagging of the dorsal vertebrae had increased. There was generalized tenderness to deep pressure over the whole thorax, and slight tenderness was noted in the upper part of the dorsal region of the spine and over the right scapular region. The lungs were clear and resonant, and there was no apparent mediastinal involvement. A soft systolic murmur had developed at the apex without axillary transmission. The pulse rate was 102. The blood pressure was 96 systolic and 76 diastolic.

The abdomen had become more prominent and somewhat firm. Tenderness to deep pressure was present under both costal margins, and there was voluntary rigidity in the epigastrium. The back was held rigid. There was moderate pitting edema of both ankles. The reflexes had become hyperactive. No neurologic signs were evident.

The patient was discharged from the hospital in August 1936. After his discharge he was frequently observed; blood counts and urinary analyses were made, and blood pressure readings were taken. The patient's condition remained about the same until April 10, 1937, when his difficulty in breathing became more pronounced; pain in the neck, in the shoulders and in both legs became more intense, and so did the pain in the left side of the neck and the jaw. Difficulty in swallowing appeared as a new symptom. He again entered the hospital on April 17.

Examination at this time showed a fairly well developed and nourished man in considerable respiratory distress. His face was cyanotic and his neck diffusely swollen. Excursions of the nasal alae were pronounced. The skin was warm and moist. The arms, the abdomen and the wall of the chest were of a bronze color. The scleras were slightly yellow. There was tenderness at various points on the scalp, as well as some irregularity, but no definite soft spots were noted. Near the hair line on the forehead there were several small firm lumps about the size of a pea. There was bilateral edema of the neck with a feeling of induration. There were scattered nodes, the size of large lima beans, tender, fixed and irregular, particularly in the submaxillary region. The chest appeared symmetric, but there was marked tenderness of the whole thoracic wall to palpation. The breast bone was protuberant. The breath sounds appeared normal, and no rales were heard. Heart sounds were apparently normal. The abdomen was distended and firm, no tenderness was elicited, with the exception of a small tender area at the right costal margin, and no masses were felt. The liver, the kidneys and the spleen were not apparently enlarged. The reflexes were hyperactive. The Babinski sign was equivocal on both sides. Cyanosis of the extremities was noted. Along the long bones there was considerable tenderness to pressure. On the day after admission the patient's condition was unchanged except that there appeared an increase of difficulty in breathing. The Wassermann test was negative.

On April 19 the dyspnea became more pronounced; the pulse was weak and irregular, and difficulty in swallowing added to the patient's discomfort. In the days following, pain in the head and the neck with no typical distribution, cyanosis, dyspnea, delirium, dysphagia, sudden rises in temperature and increased bronzing of the skin preceded death, which occurred on April 28.

Autopsy (Dr. G. H. Klinck Jr.).—The body was that of a white man 58 years of age, 63 inches (157.5 cm.) in length, well developed and well nourished. It was warm and free from rigidity. The skin had a slight yellowish tinge. There was slight edema of the lower part of the legs, and the hands appeared somewhat puffy. The hair was gray and plentiful. The eyes were light brown with pupils equal, regular and measuring 0.8 cm. in diameter. There was a moderate arcus senilis on each side. The conjunctivas were pale in general, but the inner surfaces of the lower lids showed a few minute red points suggestive of petechiae. The subcutaneous lymph nodes were not remarkable. The neck was thick and short. The submaxillary glands were not enlarged. The nasal passages and the mucous membranes of the mouth were not remarkable. The teeth were all absent and were replaced by plates. The hair over the chest and the abdomen was profuse.

There was a healed oblique surgical incision 5 cm. in length in the right lower quadrant of the abdomen. There was a healed surgical incision 8 cm. in length over the right tenth rib in the posterior axillary line. The body was opened by the usual autopsy incision. The subcutaneous fat was normally plentiful, and the muscles were of a good color. There was no subcutaneous edema.

The peritoneal cavity was free from fluid and adhesions. The diaphragm reached the level of the fifth rib on the left and the fourth on the right. The mesenteric lymph nodes could not be identified. The retroperitoneal lymph nodes were few in number and difficult to identify. The nodes found were small.

The right pleural cavity contained about 60 cc. of clear yellow fluid; the left pleural cavity, 450 cc. There were no adhesions on either side. The lungs almost completely filled their respective cavities.

The mediastinum showed nothing unusual.

The pericardial cavity contained about 30 cc. of clear yellow fluid, and its linings were smooth, pale and glistening.

The heart weighed 400 Gm. A normal amount of subepicardial fat was present. The coronary arteries were not tortuous and showed only a mild degree of sclerosis, not out of proportion to the age of the patient. The myocardium was of normal consistency, and the muscle generally was of a good red color. The lateral wall of the left ventricle was the site of numerous rather long and narrow fibrous scars which gave the muscle in this situation a fairly firm consistency. The endocardium and the valve leaflets were not remarkable. The wall of the left auricle was somewhat thicker and firmer than normal. The endocardium of the left auricle was unusually pale and appeared thickened.

The aorta presented a moderate degree of atherosclerosis, which was most marked in the abdominal portion.

The right lung weighed 450 Gm. and the left 315 Gm. Except in weight, they were almost identical. The pleural surfaces were smooth and glistening and showed the usual amount of anthracotic pigmentation. The posterior portions of both the upper and the lower lobes were collapsed, wrinkled and soft. The remaining portions of the lung tissue were gray, fluffy and air bearing. Multiple sections failed to reveal pathologic changes other than atelectasis of the posterior portions of both the upper and the lower lobes of the lungs. There was no evidence of inflammatory reaction.

The mucous membrane of the trachea was unusually pale; it was free from any evidence of inflammatory reaction. The trachea was opened anteriorly and the incision extended through the larynx. The laryngeal mucous membrane was pale. There was nothing unusual in the vocal cords. It was not possible, however, to rule out edema of the soft tissues above the vocal cords, which might have accounted for the respiratory difficulties experienced during life. The main branches of the bronchial tree were opened; the mucous membrane was pale and free from inflammation.

The thyroid gland presented nothing unusual. It was reflected on each side and a careful search made for the parathyroid glands.

Two minute masses of tissue which might have represented the parathyroid glands were found on the right side. No masses suggestive of parathyroid tissue were present on the left.

The spleen weighed 70 Gm. It was small, soft and flabby. The capsule was smooth and bluish purple. When sectioned, the parenchyma had a finely granular, reddish appearance, which did not indicate any pathologic change.

The esophagus and the stomach were not unusual. The small intestine in places showed congestion of the mucosa. Nothing else was noted. The large intestine was not remarkable. The appendix could not be identified.

The pancreas was large and firm. When it was sectioned, nothing unusual was observed.

The liver weighed 1,250 Gm. It appeared somewhat small in comparison with the size of the patient. The surface was smooth, and the organ was of normal consistency. Sections revealed slight accentuation of the hepatic markings. There was no evidence of increased translucence of the tissues which would suggest amyloid infiltration.

The gallbladder was of normal size and was thin walled; it was free from stones and contained thin yellowish green bile. All the ducts were patent.

The adrenal glands were of normal size but were somewhat softer than usual. The cortical tissues were bright yellow. The medullary tissues were clearly defined and appeared creamy white and firm.

Each kidney weighed 140 Gm. Both kidneys were surrounded by extremely pronounced perirenal capsules of fat and fibrous tissue. The renal capsules proper stripped away when the perirenal capsule was removed. The kidney surfaces presented to a slight degree a finely granular appearance and were reddish purple, as though congested. On section the normal renal markings were present. The cortical and medullary tissues were congested. There was no evidence of amyloidosis. The pelves were not remarkable. The renal arteries and their larger branches appeared free from sclerosis.

The bladder contained about 200 cc. of clear yellow fluid. The bladder wall was of normal thickness. The mucosa was pale.

The prostate gland was of normal size, and when sectioned, presented no abnormalities. The seminal vesicles were not remarkable. Grossly, the testes were normal in appearance.

The head was of normal shape and covered with a thick, heavy growth of hair. The scalp was incised in the usual manner and reflected.

The appearance of the calvarium and the bones of the skull will be described later. The calvarium was removed with some difficulty because of marked adherence to the dura.

After the calvarium was removed it was observed that almost all the inner table on the left side was adherent to the dura. This inner table appeared as a coral-like formation of spicules. The leptomeninges were not remarkable.

The brain weighed 1,330 Gm. It was of normal consistency, and the meningeal vessels contained the usual amount of blood. A mild degree of thickening of the vessels at the base was noted.

The pituitary gland was removed as soon as the brain was exposed and placed in Regaud's fixative solution exactly five hours after death. Grossly, the gland was not remarkable.

When the scalp was reflected, the calvarium presented a most unusual appearance. Innumerable, sharply circumscribed, generally circular, bright red foci, averaging 3 mm. in diameter, were present. A few larger uncircumscribed foci of redness were noted. The calvarium was unusually thin and cut with extreme ease. The edges were unavoidably broken when the calvarium was pried from the base of the skull. Some force was necessarily applied in removing the calvarium because it adhered to the underlying dura. During these manipulations the inner table of the calvarium on the left was torn away and remained attached to the dura.

When the inner surface of this bone was examined, it was observed that it presented numerous large red splotches of irregular shape and size. These were clearly seen on the right side, where the inner table remained intact. On the left side, however, the inner surface of the calvarium presented a soft, gelatinous, reddish yellow tissue as a result of detachment of the inner table. This soft tissue

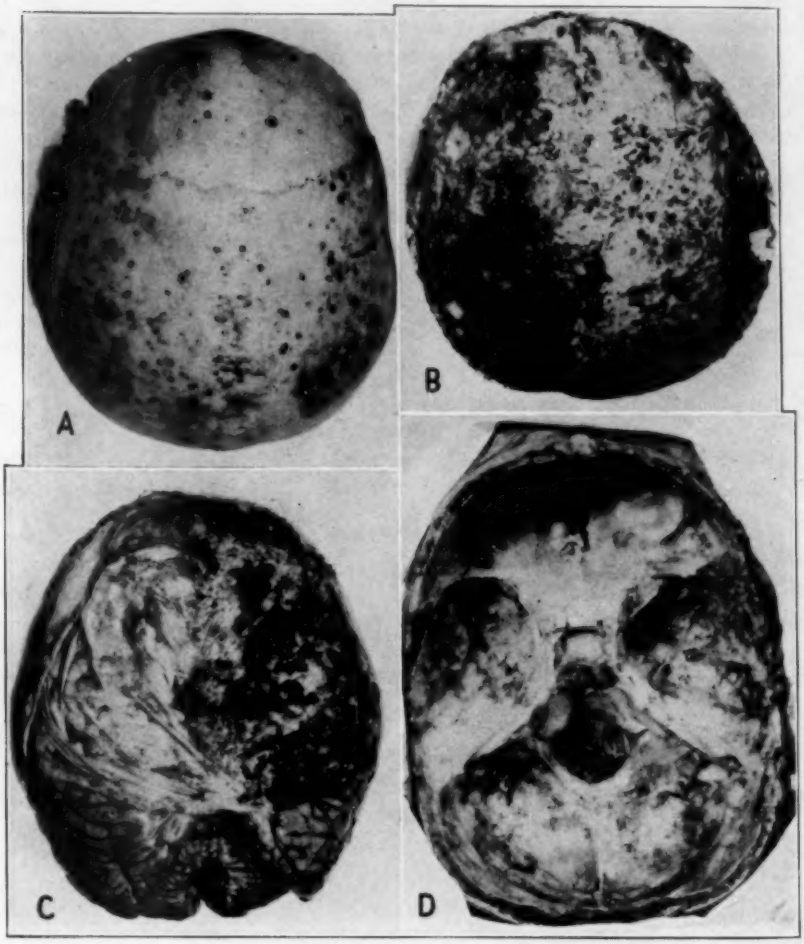

Fig. 2 (case 1).—*A*, outer aspect of the calvarium, showing innumerable foci of myeloma; *B*, inner aspect of the calcarium, showing the moth-eaten appearance of the inner table of the skull; *C*, the brain covered by the dura, showing adherence of the inner table of the calvarium on the right side; *D*, the base of the skull, showing the moth-eaten appearance of the bone due to multiple myeloma.

was characteristic of the marrow found in other bones of the body and was believed to represent the tissue of myeloma.

After the brain was removed and the dura stripped from the base of the skull, it was noted that all the bones of the base presented the same splotchy red appearance as was found on the inner surface of the calvarium. Thus it was evident that all of the bones of the skull were involved in a similar process.

Before the autopsy, the skin overlying the left clavicle was cleaned with alcohol and iodine, and the clavicle was removed under sterile conditions. A portion of this clavicle was used for animal inoculation. The cortex of the clavicle was extremely thin and, in places, even paper-like. It cut with practically no resistance. The cavity of the bone was filled with soft, mottled red and yellow tissue similar to that found in the skull. This tissue was soft, friable, translucent and, in places, almost jelly-like. It contained few spicules of bone. It was evident that the process had caused extensive absorption of bone.

The sternum was soft, and a scalpel was easily plunged through it. The marrow cavity was large and contained a dark red material similar to that found in the clavicle but of a different consistency. Marked absorption of bone had taken place, since only a few, but rather large, spicules of cancellous bone were noted. The cortex was greatly thinned out.

All the ribs were extremely thin and pliable and fractured when slight pressure was exerted on them. There was a slight deformity of the right tenth rib in the right posterior axillary line; at this site a portion of the rib had been removed in biopsy some time before.

The vertebral bodies cut with extreme ease. The intervertebral disks were not remarkable, but the cancellous spaces of the bodies presented a dark red appearance. A few rather large spicules of cancellous bone were left, but extensive absorption of bone had taken place. The tissue beneath the spicules of bone was soft, friable and intensely red. No other bones were examined.

The provisional anatomic diagnoses were: multiple myeloma; slight bilateral atelectasis; bilateral hydrothorax, and sclerosis of the left ventricular myocardium.

Examination of the Brain After Hardening in Formaldehyde Solution (Dr. G. H. Klinck Jr.).—Except for the changes resulting from fixation in solution of formaldehyde, there were no changes in the brain other than those noted when the brain was fresh. The brain was further examined by making numerous parallel frontal sections. These sections showed that the white and the gray matter of the brain were normally disposed. There was no enlargement of the ventricular system. The ependyma was smooth throughout. The choroid plexuses were without change. Multiple sections through the midbrain, the cerebellar hemispheres and the medulla revealed nothing of note.

Microscopic Examination (Dr. G. H. Klinck Jr.).—Heart: The larger branches of the coronary arteries in the subepicardial fat revealed moderately advanced atherosclerosis. No calcification was noted in sections of the vessel studied.

The myocardial fibers were of normal size and in general seemed well preserved. The branches of the coronary arteries deep within the myocardium showed numerous foci of hyaline degeneration in their walls. Other hyaline changes occurring in the connective tissues of the heart will be described later. A slightly increased amount of fibrous connective tissue surrounded the intramuscular coronary branches. In some places this fibrous tissue had extended out to replace a few of the muscle cells. Aside from these and a few other foci of fibrous tissue replacement, the myocardium showed nothing unusual.

Extremely well marked foci of hyaline degeneration were found in almost all the connective tissues of the heart. This change was characterized by the presence of large and small, irregularly shaped, branching masses of dense, clear, some-

what acidophilic, structureless substance. This change was apparent in the subepicardial connective tissue as well as in the subendocardial connective tissue and in the connective tissue throughout the heart. It was most marked in the subendocardial tissues. This hyaline change, while not uncommon in connective tissue, was extremely marked in this case. A similar hyaline degeneration could be observed in almost all the branches of the coronary arteries within the myocardium as well as in the subendocardial and the subepicardial connective tissue. In some cases it appeared as though muscle fibers of the heart were being replaced by this hyaline substance, but careful examination revealed that the changes were occurring solely in connective tissue. Examination of a section of the wall of the left auricle revealed that the endocardium was loose in structure and much thickened.

Aorta: The sections studied revealed little of note. The submesothelial connective tissue of the adventitia was infiltrated by moderate numbers of small round cells which appeared to be lymphocytes. The vessels of the adventitia had unusually thick walls but were free from perivascular infiltration. In some of the vessels there was a suggestion of hyaline change.

Trachea: A section of the upper portion of the trachea showed marked edema of the connective tissue outside of and within the cartilaginous rings. The edema was most marked in the latter site. The connective tissue of the trachea showed slight hyaline degeneration. A large portion of the epithelial lining of the trachea was absent, but this was interpreted as a result of postmortem change or artefact. Nevertheless, well marked subacute tracheitis was present. The subepithelial connective tissue, in addition to edema, revealed the presence of numerous lymphocytes and a moderate number of polymorphonuclear leukocytes, the majority of which were eosinophils. The changes just described possibly account for the respiratory distress experienced by the patient shortly before death.

Lungs: In all sections of lung studied there was slight thickening of the connective tissue of the pleura, and in places hyaline degeneration was noted. Mild acute bronchitis and bronchiolitis were present. The branches of the bronchial tree contained varying numbers of polymorphonuclear leukocytes, and in some instances the walls of the tubes were mildly inflamed. Some sections of lung showed partial collapse of the alveoli. In these situations the remaining air spaces contained small numbers of polymorphonuclear leukocytes. In other sections of lung the pulmonary tissues themselves were mildly inflamed. These changes were interpreted as representing pneumonitis rather than real pneumonia. There was no evidence of myeloma in any of the sections studied. A few alveoli contained large numbers of polymorphonuclear leukocytes, fibrin and a few erythrocytes. The lungs in general showed mild pneumonitis, but in a few places there was early bronchopneumonia.

Diaphragm: Sections of the diaphragm revealed no changes worthy of note. No infiltration of plasma cells was noted.

Spleen: The capsule of the spleen was not remarkable. The splenic sinusoids contained normal numbers of erythrocytes. The splenic pulp was cellular, but no abnormal cells were noted. The usual degree of thickening of the arterioles of the spleen was observed.

Gastrointestinal Tract: Sections of the stomach, the small and the large intestine revealed no abnormalities.

Pancreas: Histologically, the pancreas presented nothing unusual. The islet tissue was plentiful and was normal in appearance. The acinar cells were well preserved.

Liver: The tissues of the liver presented nothing worthy of note histologically. The parenchymatous cells were unusually well preserved. The sinusoids contained the usual number of erythrocytes. The portal canals and associated structures were not remarkable. No infiltration of plasma cells was present in the sections studied.

Adrenal Gland: A section of one adrenal gland revealed that the cells were unusually well preserved. The gland was divided into the usual zones. The adjacent fatty and fibrous tissues showed numerous foci of hyaline degeneration. This change was also noted in some of the blood vessels in the vicinity.

Kidneys: In the kidneys a few small subcapsular scars were observed. These consisted of dense fibrous tissue infiltrated by varying numbers of lymphocytes. The renal tissues in general showed little worthy of note. The glomeruli were unusually well preserved. The vascular systems of the kidneys were unchanged. The renal pelves were not unusual.

Bladder: The vesical mucosa was thin but intact throughout. No evidence of inflammatory reaction was noted.

Prostate Gland: A mild degree of benign glandular hyperplasia was present. A few of the acini contained small numbers of polymorphonuclear leukocytes, and the walls of these acini were mildly inflamed. The section included a portion of a seminal vesicle, but this was not remarkable.

Testicle: A section of one testicle revealed slight edema of the interstitial tissues. The majority of the tubules were well preserved, but some of them were sclerosed. Spermatogenesis had been taking place.

Peribronchial Lymph Nodes: Sections of two peribronchial lymph nodes revealed rather large deposits of anthracotic pigment. The tissues of the gland were moderately sclerosed, and the lymph sinuses were in some instances considerably dilated. A normal number of plasma cells was scattered through the glands, but the presence of these cells was not interpreted as infiltration by myeloma.

Parathyroid Gland: Sections taken from blocks of tissue were thought possibly to contain parathyroid tissue and were examined. These blocks showed only connective tissue and thyroid gland substance. There was no evidence of parathyroid tissue in any of the sections studied.

Thyroid Gland: Sections of the thyroid gland revealed the acini to be large and the lining epithelium to be flat. A few foci of chronic inflammation were present. These changes were interpreted as representing early colloid goiter.

Voluntary Muscle: A section of voluntary muscle revealed no unusual changes.

Bone Marrow: The marrow of the clavicle, the ribs, the vertebra, the sternum and the calvarium was studied. In all instances the same changes were noted. Considerable absorption of bone had taken place, and in some places this was extremely marked. It was noted, however, that the changes which were primary in the bone marrow did not extend into the adjacent soft tissues.

The site of hemopoietic tissue was occupied by large masses and anastomosing cells, which were generally of one type. The amount of fat tissue was markedly reduced by overgrowth of these cells. The type cell was rather uniform in size and, roughly, about twice the size of an erythrocyte. The cells were rarely round. Most frequently they were oval with a tendency to a rectangular shape. The rectangular-appearing cells were most numerous where the cells were assembled in dense masses. The cytoplasm of these cells was rather homogeneous, slightly eosinophilic and somewhat variable in amount. The nucleus was almost invariably located in an eccentric position. In the large majority of cells it

showed a peripheral arrangement of coarse clumps of chromatin. These cells were typical plasma cells.

Although the hemopoietic tissues were largely replaced by these plasma cells, there was evidence of remaining hemopoietic tissue. Here and there myelocytes and metamyelocytes as well as rare mature polymorphonuclear leukocytes were seen. The amount of this tissue, however, was markedly reduced compared with the normal. Furthermore, there was evidence of erythropoiesis. In some places, where plasma cell infiltration was less marked, well formed normoblasts were present. Thus, in spite of the fact that the marrow was largely replaced by plasma cells, there was evidence of functioning bone marrow.

Fig. 3 (case 1).—Roentgenogram of the skull, showing extensive localized areas of destruction.

Dura Mater: A section of the dura showed the inner table of the calvarium firmly adhering to it. The marrow of the calvarium was firmly adherent also, and this showed changes similar to those described before.

Brain: The brain substance proper was not unusual. The subarachnoid vessels, especially those about the base of the brain, had slightly thickened walls. A section of the basilar artery revealed moderate thickening of its walls. The ependyma and the choroid plexus were normal.

Spinal Cord: Sections of the upper cervical portion of the spinal cord revealed no remarkable changes.

Anatomic Diagnoses.—The clinical diagnoses had been: multiple myeloma with metastasis to the mediastinum and to bones; questionable amyloidosis of the kidneys (because of the congo red test); chronic nephritis; chronic passive congestion of the liver; secondary anemia; Bence Jones proteinuria.

The final anatomic diagnoses as approved by Dr. Arthur W. Wright were: multiple myeloma; subacute tracheitis; edema of the trachea; acute bronchitis; mild terminal pneumonia; slight bilateral atelectasis; bilateral hydrothorax; mild sclerosis of the left ventricular myocardium; hyaline degeneration of the connective tissues of the heart, the aorta and the diaphragm; generalized hyaline degeneration of the arteries and the arterioles.

Report of Roentgen Observations.—March 24, 1936: The bodies of the sixth, the eighth and the twelfth dorsal vertebrae and that of the third lumbar ver-

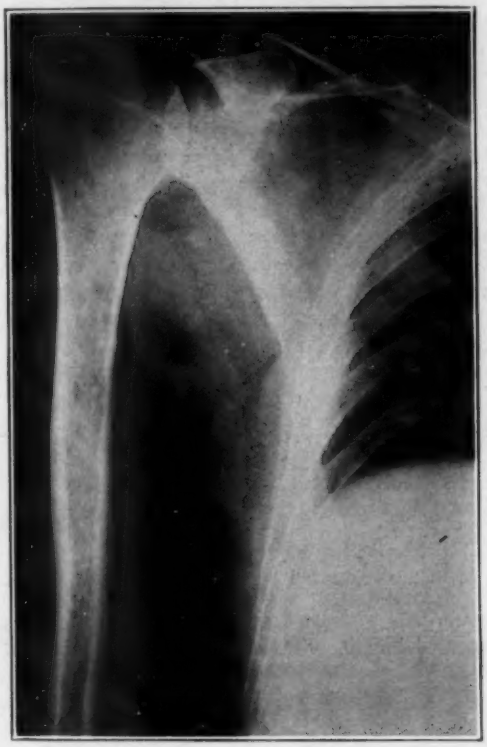

Fig. 4 (case 1).—Dorsal view of the left side, showing extensive localized destruction in the clavicle, the spine of the scapula, the humerus and the ribs.

tebra showed evidence of partial collapse. There were marked atrophic changes in all the vertebral bodies and in the ribs. There was some enlargement of the distal end of the tenth rib on the right side of the chest.

These observations were consistent with hyperparathyroidism. There was no evidence of metastatic tumor in the pelvic bones or the hips. The pelvis showed uniform changes throughout.

April 8: There were many disseminated areas of decalcification scattered throughout the skull and in the body and the ramus of each mandible. These changes were consistent with hyperparathyroidism, although it was impossible to exclude metastatic new growth entirely.

There were no remarkable changes in the lower third of either the radius or the ulna or in the bones and the joints of the wrists and the hands.

April 10: Under fluoroscopic control, the area of cystlike expansion in the eleventh rib was localized by means of two hypodermic needles, one placed on the upper border of the rib at the anterior portion of the expansion and the other under the lower portion of the rib at the posterior portion of the expanded area on the right side of the chest.

May 25: There were multiple disseminated areas of decalcification throughout the skull; these suggested metastatic tumor. A comparison with the films of April 8 revealed no definite change. The thorax was foreshortened because of multiple collapse of the dorsal vertebrae. The mediastinum was not unusual in width. The trachea did not appear to be displaced. There was evidence of multiple metastatic nodules in both clavicles and in the ribs.

September 8: There were extensive localized areas of destruction throughout the skull, through the right clavicle and the right humerus and in the ribs on both sides of the chest. There was multiple collapse of the dorsal vertebrae. There were marked atrophic changes in the lumbar part of the spine and the pelvis, but there was no definite evidence of involvement by tumor. In the shaft of the right femur there were no abnormalities.

April 19, 1937: There were extensive localized areas of destruction throughout the skull, in both clavicles and through the spine of the scapulas, in each humerus, through both radiuses and ulnas and in the ribs, suggesting a metastatic tumor. There was evidence of multiple collapse of the dorsal vertebrae.

There was evidence of multiple areas of destruction in each femur. The tibias and the fibulas and the bones of the feet were not remarkable. The bones of the hands showed generalized atrophic changes, but there was no definite evidence of tumor.

A comparison with the roentgenograms taken Sept. 8, 1936, revealed a definite increase in the amount of destruction.

CASE 2.—R. H., a railroad brakeman 44 years old, entered the Albany Hospital complaining of pain in the left groin "running down" to the knee.

History of Illness.—Eight weeks before admission he noted a sharp pain in the left groin which caused him to limp, and though it did not bother him a great deal, it interfered with his work. It was intermittent and was not increased by walking or exercise. Lately the pain had been more constant and more severe. For three weeks before admission it had radiated to his back, to the upper part of his left leg, to his left knee and to the upper portion of the lower part of the leg. The pain came without warning and was severe enough to keep him awake at night. He stated that concomitant with the sharp pain in his left groin eight weeks before admission, he had noted a small "lump" in the groin. This was about the size of an almond, and it had increased somewhat in size since then. He believed that the pain emanated from this lump, otherwise the latter gave him no trouble.

For eight years he had been receiving treatments for albuminuria, which was discovered by a routine railroad examination. He apparently had no symptoms relating to the urinary tract except a slight burning at the end of the penis on urination.

Past History.—Except pleurisy when he was 12 years of age, he had had no other serious illnesses, accidents or operations.

A review of the systems showed them to be essentially normal, except for albuminuria.

Familial History.—The father died of "stomach trouble"; the mother died from "stroke." Two of his brothers were dead; one from "kidney trouble" and the other from diabetes.

Examination.—The patient was a well developed and well nourished, stout man, 44 years of age, who walked with a slight limp. The skin and the mucous membranes were pale and the eyelids slightly puffy. The pupils were equal and regular and reacted to light and in accommodation. The ears, the nose, the mouth and the teeth were essentially normal. A few small and freely movable cervical glands were noted. The thorax, including the heart and the lungs, was apparently normal. The abdomen was obese; no masses were detected in it, and no tenderness or spasticity was noted. The liver and the spleen were not enlarged. In the left groin there was a hard immobile regular mass the size of an English walnut, firmly attached to the underlying tissues, painless and located in the lowest portion of the inguinal canal. Apparently, it was attached to the pelvis. There was no impulse on coughing or weakness of the abdominal rings. There was weakness of the left leg with pain on motion in the suprapubic and lower inguinal regions. There was pain in the left buttock and in the left knee on motion. No definite involvement of the left sciatic nerve was noted.

The neurologic examination gave essentially negative results. The reflexes were negative; there was no Romberg sign or clonus. Measurements of both legs were equal.

Rectal examination revealed a slightly enlarged, smooth and rather hard prostate gland. The left lobe was slightly larger than the right, and an attached mass the size of a sickle pear, immobile and painless on palpation was noted; it was apparently attached to the left pubic bone. There were no enlarged inguinal glands. (The tumor just described was apparently not a lymph gland.)

Cystoscopic examination showed no evidence of tumor formation, though along the left margin of the vesical neck there was edema with several large tortuous veins on the lateral wall. The left lateral wall showed moderate extravesical pressure, and the urethral ridge was elevated. The urethra was not depressed, and cystoscopic examination revealed less deformity of the bladder than would be suspected from the cystogram.

No growth of bacteria was obtained from the blood culture.

From the cavity of the right fifth rib Bacillus coli was isolated. From the abscess of the pubic bone a gram-negative bacillus which does not belong to the known group of pathogens was isolated.

The results of the examination of the blood and the urine are given in table 7. The roentgenologist's report is given on page 991.

A tentative diagnosis of malignant tumor of the pelvic bone, probably sarcoma, was made.

Treatment and Course.—The patient was discharged from the hospital fourteen days after admission.

In the meantime high voltage roentgen therapy had been instituted.

Three months later, the patient was advised to return to the hospital. At this time there was excruciating and almost continuous pain in the arms and the legs. During his stay of five days in the hospital, further roentgenograms were taken of the pelvic bones, the right femur, the skull and the ribs. The urine was again examined for Bence Jones protein (table 7). No loss of weight had been noted, and a general physical examination showed the patient's condition to be

about the same as on first admission. The mass in the groin had not apparently enlarged, and again the tentative diagnosis of malignant tumor of the pelvic bone with metastasis to the skull and the ribs was recorded.

Three weeks later the patient reentered the hospital because of the severity of the pain in the ribs, the sternum, the shoulders and the back and because of the presence of a "tumor of the head." This was an egg-sized mass located in the right frontoparietal region of the skull; it was of bony hardness with scattered areas of fluctuation and was painless to pressure. The overlying skin appeared to be uninvolved. Tenderness was elicited over the left mastoid and occipital regions, over both shoulders, the upper dorsal portion of the spine, the sternum, the lower left ribs, the right costal margin, the left pubic bone and both femurs. Over the superior ramus of the left pubic bone was a fixed, firm, tender mass about the size of a lemon.

Biopsy of the growth in the skull was performed on the day after admission. Dr. Arthur W. Wright reported the biopsy as follows: "This is a fairly rapidly growing malignant tumor, which diffusely infiltrates the scalp. The neoplastic cells are poorly differentiated but appear epithelial. They do not form any recognizable structure. The tumor is believed to be metastatic, but the source of the primary neoplasm cannot be determined."

The course of high voltage roentgen therapy was continued, but in spite of all treatment the patient died one month after his last admission.

Autopsy (Drs. J. W. Conrad and E. F. Joslin).—The body was that of a white man, well developed and apparently well nourished. He was said to be 44 years of age and appeared to be approximately that age. The body measured 66 inches (165 cm.) in length. There was no edema, but there was slight dependent lividity. The hair was gray and sparse. Through the scalp in the right frontoparietal region, about 10 cm. lateral to the midline, was an incision in the sagittal plane. It measured 2 cm. in length and was covered with a brownish black crust. The eyes were gray. The pupils were equal and round and measured 0.7 cm. in diameter. The nose and the ears were normal. The teeth anteriorly were in good condition, but the mouth could not be opened far enough to ascertain their condition posteriorly. The skin was of normal texture. There was a depressed irregular oval scar, measuring 2 by 3 cm. on the middle of the lateral aspect of the left arm. On the middle of the medial aspect of the right forearm there was a tattoo in red and blue colors of two clasped hands holding a sheaf of palm leaves (?); this measured about 4 by 7 cm. in its greatest diameters.

The body was opened by the usual midline incision from the sternal notch to the symphysis pubis. There was adipose subcutaneous tissue measuring 1 cm. over the chest and 2.5 cm. over the abdomen. The muscles were of the normal dark red color.

The diaphragm reached the level of the fourth rib on the right and the fourth interspace on the left. There was no free fluid, and on gross examination the peritoneum appeared normal. There were no palpable adhesions.

The right pleural cavity was free from fluid. There were no adhesions. Grossly, the pleura presented a normal appearance. The left pleural cavity also was free from fluid. There were a few strands of fibrous tissue between the parietal and the visceral pleura in the region of the apex of the upper lobe of the left lung. These broke with ease. Elsewhere the pleura was smooth and glistening.

The structures of the mediastinum appeared grossly normal on first examination, but subsequent dissection showed that there was a firm nodular mass of tissue in the arch of the aorta, which cut with some difficulty, the knife blade grating on calcareous granules. The cut surfaces presented a rather firm, everting whitish yellow tissue interspersed with soft caseous bluish green material.

The pericardial cavity contained about 25 cc. of clear straw-colored fluid. There were no adhesions. The linings were smooth and glistening.

The heart weighed 370 Gm. The size was compatible with the size and age of the subject. There was an increased amount of subepicardial fat, especially over the right ventricle. The heart felt somewhat softer than normal and cut with decreased resistance. The myocardium was pale. That of the right ventricle measured 0.8 cm. and that of the left ventricle 1.8 cm. in thickness. The endocardium and the valve leaflets appeared normal. The circumferential measurements of the heart valves were tricuspid, 10.5 cm.; pulmonic, 7 cm.; mitral, 10 cm., and aortic, 7 cm.

In the aorta there were no ulcerations or foci of calcification. There was a suggestive slight wrinkling of the intima in the lower abdominal portion, but is was hardly definite enough to be termed sclerosis.

The left lung weighed 430 Gm. The pleural surfaces were smooth and glistening, except in the apical region, where there were the adhesions already mentioned. Beneath the pleural surfaces were the blackish mottlings of anthracosis. The upper lobe of this lung felt as if it was of normal consistency throughout; the lower lobe posteriorly was dark purple and firm, and on section the vesicular tissue had a purplish black color and was meaty in consistency. There was a small firm whitish nodule, about 0.75 cm. in diameter, in the tissue of the lateral costophrenic tongue of the lower lobe. This sectioned with ease, and the cut surfaces presented a homogeneous everting firm whitish tissue. The bronchial tree was opened but presented nothing of note.

The right lung weighed 490 Gm. and was similar to its fellow except that there were no adhesions and no nodule was palpable in the parenchyma.

The spleen weighed 220 Gm. The capsule was of normal color and thickness but was somewhat wrinkled. The spleen was soft to touch and cut with decreased resistance. The cut surfaces presented a dark red appearance.

The esophagus was of normal size and shape. The muscular wall and the mucosa were essentially normal. The stomach presented nothing of note on the serosal surface. The mucosa was diffusely reddened and velvety. There were no ulcerations or nodules. The stomach contained a few cubic centimeters of light brownish yellow fluid.

The small and the large intestine presented a normal appearance. The appendix was 5 cm. in length, less than 0.25 cm. in diameter and of a whitish color and firm consistency.

The pancreas appeared normal.

The liver weighed 2,100 Gm. Its edges were less sharp than normal. The capsule was thin and glistening. The liver appeared somewhat pale. It sectioned with ease, and the cut surfaces presented yellowish brown parenchyma in which the markings were distinct. There were no nodules and no increase in fibrous tissue.

The gallbladder was of normal size. It was greenish black and contained no calculi, but about 5 cc. of greenish black thick bile was present. The mucosa showed postmortem erosion. The bile ducts were patent.

The adrenal glands were buried in dense adipose tissue but presented normal characteristics grossly.

The right kidney weighed 155 and the left 170 Gm. The kidneys appeared slightly small. The capsules were of normal thickness and stripped with ease, displaying fine granular cortical surfaces. There were approximately ten cortical cysts, averaging 0.8 cm. in diameter and containing whitish serous fluid within thin walls. The kidneys sectioned with normal resistance. The cortical surfaces were pale and displayed marked pinpoint reddening of the glomeruli. Grossly, the medullas presented nothing of note. There was an increase of pelvic fat.

The bladder contained about 100 cc. of cloudy yellow urine. The bladder wall was somewhat thick. The mucosa was normal.

The median lobe of the prostate gland was enlarged and bulged somewhat into the bladder. The limits of the gland could not be defined because the capsule

TABLE 7.—*Data ... Patient in Case ...*

Data	Wassermann Tests: Blood: Cholesterolized Antigen	Wassermann Tests: Blood: Acetone Insoluble Antigen	Wassermann Tests: Blood: Precipitin (Kahn)	Wassermann Tests: Spinal Fluid	Blood Pressure, Mm. of Mercury	Blood Counts: Hemoglobin, per Cent	Blood Counts: Red Blood Cells	Blood Counts: Color Index	Blood Counts: White Blood Cells	Blood Counts: Differential Count: Polymorphonucleares	Blood Counts: Differential Count: Eosinophils	Blood Counts: Differential Count: Basophils	Blood Counts: Differential Count: Lymphocytes	Blood Counts: Differential Count: Myelocytes	Blood Counts: Differential Count: Undetermined	Reaction	Specific Gravity	Albumin
3/ 2/36	..	..	..	..	120/80	97	4,950,000	1.0	9,200	68	0	0	28	4		Acid	1.018	0
3/ 4/36	..	—	—	..	.....	..	.....	...	.....	..	..	..	..	..		.....	.....	..
3/ 6/36	—	—	—	..	.....	103	5,350,000	0.9	10,800	75	2	..	18	5		.....	.....	..
3/ 9/36	..	..	..	— with all quantities	.....	..	.....	...	.....	..	..	..	..	..		.....	.....	..
3/11/36	—	—	—	..	.....	..	.....	...	.....	..	..	..	..	..		.....	.....	..
5/ 6/36	..	..	..	..	.....	..	.....	...	.....	..	..	..	..	..		.....	.....	..
6/ 4/36	..	..	..	..	.....	..	.....	...	.....	..	..	..	..	..		Acid	1.017	0
6/15/36	..	..	..	..	130/84	..	.....	...	.....	..	..	..	..	..		.....	.....	..
6/16/36	..	..	..	..	.....	..	.....	...	.....	..	..	..	..	..		Acid	1.021	0
7/14/36	..	..	..	..	.....	75	4,150,000	...	15,220	82	1	..	13	4		Acid	1.012	2+
7/29/36	..	..	..	..	.....	..	.....	...	.....	..	..	..	..	..		Acid	1.018	2+
8/ 5/36	..	..	..	..	.....	..	.....	...	.....	..	..	..	..	..		Acid	1.014	3+
8/11/36	..	..	..	..	.....	..	.....	...	.....	..	..	..	..	..		Acid	1.017	3+

had been destroyed by a firm dense whitish yellow friable tumor, which spread laterally and anteriorly to involve the pubic bones. When the gland was sectioned, several small pockets of thick yellow purulent material were encountered; some of this material was taken for culture. The inner aspects of the pubic bones were necrotic, and spicules of bone were palpable within the neoplastic tissue. The rectum was not involved by the growth.

Grossly, the genitalia presented normal characteristics.

The vertebral bodies of the thoracic portion of the spine presented slight nodular projections from their anterior surfaces. When sectioned, the vertebral bodies cut with ease, and the incised surfaces exhibited the same type of firm whitish yellow friable homogeneous neoplastic tissue already found about the prostate gland. All the ribs were studded with firm nodules of the same tissue. The ribs broke on slight pressure. In several instances the centers of the tumor nodules were necrotic and fluid in consistency.

The provisional anatomic diagnoses were: primary carcinoma of the prostate gland; metastatic carcinoma of the skull, the ribs, the left lung, the vertebrae and the pelvis; chronic vascular nephritis; atelectasis of the lungs; acute gastritis; anthracosis; cortical cysts of the kidneys.

Microscopic Examination.—Heart: The epicardium contained a large amount of adipose tissue, which extended along the connective tissue trabeculae into the myocardium for a short distance. In one section, a large coronary artery was partially occluded by irregular large fibrosed atheromas. There was slight separation of the muscle fibers of the left ventricle by fluid. The smaller blood vessels of the myocardium were congested throughout. No tumor nodules were seen. The endocardium was not remarkable.

E 7.—Data ... *e Patient in Case 2*

Urine									Bacteriologic Examination						Phenolsulfonphthalein Test	
									Bladder		Left Kidney		Right Kidney			
Reaction	Specific Gravity	Albumin	Sugar	Acid	Diacetic Acid	Blood	Hyaline Casts	Bence Jones Protein	Smear	Culture	Smear	Culture	Smear	Culture	Specimen 1 (Volume, 110 Cc.)	Specimen 2 (Volume, 70 Cc.)
Acid	1.018	0	0	0	0	Occasional red and white cells	0	0	0	0	..	..	..	.....	18% excreted	17% excreted
.....	.....	..	..	..	..	.....	.....	..	..	..	0	0	..	.....	.....	.....
.....	.....	..	..	..	..	.....	.....	..	..	..	..	..	..	.....	.....	.....
.....	.....	..	..	..	..	.....	.....	..	..	..	..	..	0	Staphylococcus albus	.....	.....
.....	.....	..	..	..	..	.....	.....	..	..	..	..	..	..	.....	.....	.....
.....	.....	..	..	..	..	.....	.....	0	..	..	..	..	..	.....	.....	.....
Acid	1.017	0	0	0	0	.....	.....	..	..	..	..	..	..	.....	.....	.....
.....	.....	..	..	..	..	.....	.....	..	..	..	..	..	..	.....	.....	.....
Acid	1.021	0	0	0	0	.....	.....	0	..	..	..	..	..	.....	.....	.....
Acid	1.012	2+	0	0	0	.....	Finely granular casts	0	..	..	..	..	..	.....	.....	.....
Acid	1.018	2+	0	0	0	Occasional red and white cells	Few casts	0	..	..	..	..	..	.....	.....	.....
Acid	1.014	3+	0	0	0	Few white cells	Few casts	0	..	..	..	..	..	.....	.....	.....
Acid	1.017	3+	0	0	0	Few white cells	Few casts	0	..	..	..	..	..	.....	.....	.....

Aorta: The intima of the aorta showed no atheromas or lipoid deposits. The fibers of the media were separated throughout, apparently by edema.

Lungs: The lungs were slightly congested. The pleural surfaces were not remarkable. The increased size of the alveolar air spaces in some sections suggested slight emphysema. The bronchioles showed moderate desquamation of their epithelial cells. There was little anthracotic pigmentation in the sections studied. No tumor tissue was visible.

Mediastinal Lymph Node: The mediastinal lymph node was composed of calcified and caseous foci surrounded by hyalinized scar tissue in which anthracotic pigment was present. Outermost was a layer of vascular connective tissue in which were many leukocytes, plasma cells, polymorphonuclear leukocytes and endothelial phagocytes laden with brown and black pigment granules. This undoubtedly represented long-standing healed calcified caseous tuberculous lymphadenitis.

Spleen: The capsule of the spleen was moderately thickened by dense hyaline connective tissue. There was marked congestion of the pulp, and areas of scattered hemorrhage could be seen. About these foci were large phagocytic cells stuffed with golden brown pigment from the degenerating red cells. An increased number of polymorphonuclear leukocytes was noticed throughout.

Gastrointestinal Tract: The mucosa of the stomach showed postmortem fragmentation. The mucosal, muscular and adventitial layers exhibited the loose arrangement indicative of edema. The blood vessels were congested. There was no cellular infiltration. Other portions of the intestinal tract showed similar changes.

Pancreas: In some acini of the pancreas large foci of postmortem degeneration were present. The islet cells were not unusual in appearance. The interlobular and the interacinar connective tissue was loose and edematous.

Liver and Gallbladder: The liver capsule was of normal thickness. The hepatic sinusoids were congested throughout, but there was no cellular infiltration. Some of the endothelial cells were laden with golden pigment granules. The parenchymal cells showed early postmortem degenerative changes. In some lobules, fat vacuoles of various sizes and an increased amount of golden brown pigment within the hepatic cells were observed. The portal spaces were not remarkable.

The gallbladder showed postmortem degeneration of the mucosa. The other portions of the wall were normal.

Adrenal Glands: In the adrenal glands the cortical and the medullary cells demonstrated the changes of early parenchymatous degeneration. The interstitial connective tissue throughout was loose, edematous and congested.

Kidneys: The capsules of the kidneys were of normal thickness. There were scattered foci of sclerosis with lymphocytic infiltration here and there through the cortices. The glomerular capillaries were congested, and many showed proliferation and fibrosis of Bowman's capsules. In and near the scarred foci many of the glomeruli were completely changed into masses of dense hyaline connective tissue. Intermediate stages of this change also were observed. The epithelial cells of the tubules in both the cortical and medullary portions showed both postmortem and parenchymatous degeneration, and many of the cells were desquamated and lay free in the lumens. Many of the collecting tubules contained small hyaline casts. The connective tissue stroma throughout the kidneys was increased, loose and edematous. The smaller blood vessels were congested. The larger blood vessels had slightly thickened intimal coats. The renal changes were those of mild chronic vascular nephritis.

Prostate Gland: Sections from the prostate gland showed rather advanced postmortem degenerative changes. The acinar epithelium was desquamated, and the smooth musclar stroma was fragmented. The most significant change was the presence in several sections of a cellular, poorly differentiated malignant neoplasm which was not epithelial in type. Most of the tumor was necrotic, and in some spots fibrosis was marked. In those places where the cells were viable, they were observed to be small, round and hyperchromatic, resembling lymphocytes. They grew in nestlike groups. The histologic appearance and the location of the neoplasm indicated that it was not a primary prostatic tumor but rather a secondary growth which reached the prostate gland by direct invasion.

Altogether, taking into consideration the histologic and cytologic characteristics of the new growth and the gross evidence of extensive bone involvement, Dr. Conrad expressed the opinion that the tumor was primary myeloma of the lymphocytic type which had infiltrated the prostate gland from the adjacent pubic bone.

Bone: Sections from the pubic bone as well as from several ribs and vertebral bodies showed extensive invasion of the bone marrow by a primary bone marrow neoplasm. The neoplastic cells were small, shrunken and hyperchromatic, often resembling lymphocytes. They invaded and replaced the normal marrow and in places were associated with the production of much dense connective tissue. Where tumor growth was most active, fibrosis was least marked and necrosis of the tumor cells was abundant. Where growth was oldest and slowest, fibrosis was most prominent. The character of the growth was the same in all sections, although in the pubic bone there was more fibrosis than in the vertebrae or the ribs.

The tumor was considered to be primary myeloma of bone. It was of the lymphocytic type. This is the type of tumor which many European pathologists call primary lymphosarcoma of bone.

Fig. 5 (case 2).—Roentgenogram of the pelvis, showing local destruction of the superior ramus of the pubic bone on the left side and the mass displacing the bladder toward the left.

Anatomic Diagnoses.—The clinical diagnosis had been: generalized carcinomatosis of unknown origin.

The final anatomic diagnoses as approved by Dr. Arthur W. Wright were: multiple myeloma of the lymphocytic type in the pubis, the vertebrae, the ribs and the skull; secondary multiple myeloma of the prostate gland and the lungs; mild chronic vascular nephritis; cortical cysts of the kidneys; healed tuberculosis of the hilar lymph nodes; atelectasis of the lungs; anthracosis.

Report of Roentgen Observations.—Feb. 29, 1936: There was local destruction of the superior ramus of the pubic bone on the left side extending from a point ¾ inch (2 cm.) lateral to the joint of the symphysis pubis to the hip joint. There was apparently some mass within the pelvis which displaced the bladder toward the left.

March 3: After the intravenous injection of neo-iopax, the pelvis and calices of the right kidney and the right ureter were visible and apparently normal. The

calices of the left kidney were not well filled. The transverse diameter of the left kidney appeared to be somewhat greater than that of the right. The upper half of the left ureter was visible. There was no evidence of hydroureter on the left side. There was a visible defect in the bladder in its left lower quadrant.

March 4: There is no roentgen evidence of metastatic tumor in the lungs or the separate lobes.

March 5: A pyelogram of the left kidney showed the pelvis and the calices to be normal. There was no evidence of hydroureter on the left side. The lower portion of the ureter was displaced toward the midline.

June 16: The tumor formerly seen at the superior ramus of the pubis on the left side appeared to be healed. There was no definite evidence of metastatic tumor in the right femur.

Fig. 6 (case 2).—Roentgenogram of the skull, showing large areas affected by metastatic tumor.

June 19: There were six large areas of metastatic growth in the skull. There was evidence of a metatatic tumor in the seventh rib, posteriorly on the left side.

The total dose of roentgen radiation administered was 5,550 r.

CASE 3.—H. H., a white woman 62 years of age, was first admitted to the Albany Hospital on July 22, 1934, complaining of severe pain in the lower portion of her back which radiated down to the right hip and the right leg. This pain had its onset some three months before and had not been relieved by strapping of the back. General physical examination gave an essentially negative result. The blood pressure was 140 systolic and 90 diastolic. The blood counts were normal. Chemical analysis of the blood and serologic tests gave normal results. A roentgenogram of the spine and the pelvis showed no definite pathologic

changes, although there was an increase in the lower articular portion of the body of the twelfth dorsal vertebra and the cartilage between it and the first lumbar vertebra was diminished in thickness. The only observation which it was felt might be explanatory of her symptoms was that she had unusually weak arches. She remained in the hospital for a week, and during this time arch supports were made and applied; they gave her considerable relief.

She was next admitted one month later, August 23, with the complaint of similar pain in both lower extremities, radiating from the sciatic notch down the back of the legs. Physical and neurologic examinations again yielded negative results. The blood pressure was 136 systolic and 80 diastolic. Several examinations of the blood were made, and it was found that she had a moderate amount of anemia with a persistently high color index. However, there were no findings in stained smears of the blood which could be construed as indicative of pernicious anemia. At this time the possibility of a silent growth was considered, and roentgenograms were made of the gastrointestinal tract. These disclosed no abnormalities. Since no organic disease was found to account for her symptoms, it was felt that her complaint had a neurotic basis. After rest, symptomatic care and iron therapy, her symptoms were considerably relieved, and the anemia cleared up. On September 22 she left the hospital after a month's stay with the eventual outcome still somewhat in doubt.

Approximately two months later, on November 17, the patient entered the hospital for the third time. On the morning of admission she had wrenched her right arm slightly and after this had been unable to use the member because of excruciating pain. In addition, the pain in the back and the lower extremities had recurred several weeks before and had grown steadily worse, until she had great difficulty in walking.

Physical examination at this time revealed an obvious fracture at the middle of the right humerus. The skin was rather pale. The temperature was 100 F.; the pulse rate was 98, and the respiratory rate was 22. The blood pressure was 90 systolic and 58 systolic. There were impaired resonance, increased whisper in speaking and moist rales at the base of the left lung in the midaxillary line. Active and passive motion caused severe pain in the lower lumbar region and the legs. No neurologic changes were found.

The urine for the first time showed large amounts of albumin and a few white blood cells. Blood counts were within normal limits.

Roentgenograms revealed fractures through the middle of the shaft of the right humerus, the ninth rib on the right side and the sixth, seventh, ninth and tenth ribs on the left, with evidence of a metastatic tumor in the ribs on both sides of the chest. There was evidence of thickening of the pleura on the left side toward the mediastinum about the apical portion of the lung; this thickening might have been due to neoplastic invasion or to effusion along the medial aspect of the lung. There was a partial collapse of the eighth dorsal and fourth lumbar vertebrae, and there was evidence of a metastatic tumor in the shaft of each femur just below the lesser trochanter.

The fracture of the right humerus was reduced and a molded plaster splint applied. Because of pain in the back and weakness, which now became apparent, the patient remained bedfast during the rest of her stay in the hospital. About three weeks after admission she began to complain of numbness and tingling of the feet and difficulty in moving the lower extremities. Neurologic examination at this time showed that active motion of the lower extremities was entirely lacking and that there was great diminution of muscle strength throughout both legs.

TABLE 8.—*Data on Patient in Case 3*

Date	Wassermann Tests	Blood Pressure, Mm. of Mercury	Blood Counts: Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Differential: Polymorphonuclears	Eosinophils	Lymphocytes	Myelocytes	Undetermined	Blood Chemistry: Non-protein Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Creatinine, Mg. per 100 Cc.	Bence Jones Protein	Comment
7/22/34 (1st admission)	..	140/90	89	4,430,000	8,600	..	..	..	..	..	..	..	..	..	
7/23/34	..	.....	..	.....	.....	..	..	..	..	..	43	96	..	..	
7/24/34	—	.....	..	.....	.....	..	..	..	..	..	..	..	..	..	
7/27/34	..	.....	..	.....	.....	..	..	..	..	..	46	..	..	..	
8/24/34 (2d admission)	—	.....	80	3,200,000	4,800	..	..	..	..	..	..	..	..	..	Red blood cells normal in shape
8/25/34	..	136/80	..	.....	.....	..	..	..	..	..	35	95	1.1 mg.	..	
8/26/34	..	.....	83	3,250,000	5,200	67	..	31	2	..	..	..	..	..	
8/28/34	..	.....	88	3,800,000	5,600	..	..	..	..	..	..	..	..	..	Red blood cells showed deep coloring but no marked variation in size and shape
9/ 3/34	..	....	93	4,090,000	8,200	62	1	35	2	..	..	..	..	..	Differential count practically normal
9/ 5/34	..	.....	101	5,150,000	.....	..	..	..	..	..	..	..	..	..	Differential count practically normal
9/ 9/34	..	.....	100	4,170,000	.....	..	..	..	..	..	..	..	..	..	
9/16/34	..	.....	101	5,070,000	.....	..	..	..	..	..	..	..	..	..	
11/17/34 (3d admission)	..	90/58	..	.....	.....	..	..	..	..	..	..	..	..	..	
11/18/34	..	105/60	81	4,200,000	9,200	65	2	20	10	3	..	..	..	..	
11/20/34	..	.....	..	.....	.....	..	..	..	..	..	..	..	..	—	
11/21/34	..	.....	..	.....	.....	..	..	..	..	..	..	..	..	+	
11/24/34	..	.....	..	.....	18,850	..	..	..	..	..	..	..	..	..	
12/ 3/34	..	.....	70	3,900,000	10,020	68	..	24	4	4	..	..	..	..	
12/13/34	..	.....	..	.....	.....	..	..	..	..	..	..	..	..	+	Anemia more pronounced
12/15/34	..	.....	63	3,600,000	8,900	..	..	..	..	..	..	..	..	..	

The knee jerks were diminished, and the ankle jerks could not be elicited. No pyramidal tract signs were present. There was normal sensitivity to touch. Sensation of pain was diminished over the right foot. The muscles of the calf were insensitive to deep pressure. Sense of vibration was entirely absent over the patellas, the shins and the malleoli. Sense of position was impaired bilaterally, more on the right. Heat and cold could not be discriminated over the right foot.

After this the patient's course was rapidly downhill. She had difficulty in starting urination and had to be catheterized constantly. Constipation was marked, and daily enemas were necessary. Increasingly large doses of morphine were required to control the inordinate pain. After several more weeks she complained of girdle pains across the abdomen and showed a definite level of hyperalgesia and hyperesthesia just below the umbilicus. There was increasing respiratory difficulty. The blood pressure was 105 systolic and 60 diastolic. She grew steadily weaker; the erythrocyte count and the hemoglobin value fell markedly, and death ensued on December 27, some six weeks after admission and eight months after onset.

A culture of the patient's blood on this date showed overgrowth by spreader.

Autopsy (Dr. G. H. Klinck Jr.).—The body was that of a white woman 63 years of age, 60 inches (150 cm.) in length, normally developed but undernourished. The body was warm and flaccid. There was slight lividity of the dependent portions. No edema was observed. The skin was pale and thin. The hair was brown and plentiful. The ears and nose were normal. The eyes were brown; the pupils were equal, regular and middilated. The membranes of the mouth were covered with a dirty mucoid material. All teeth were absent. The right arm was in a rather loosely fitted splint consisting of small pieces of wood and bandage. The finger tips were cyanotic. The breasts were of moderate size and free from palpable masses. Sections revealed nothing of note. The abdomen was large but not distended. There was an ecchymotic area, 4 cm. in diameter, over the anterosuperior spine of the ilium on the right. The body was opened by the usual autopsy incision. On reflecting the muscles from the thorax it was noted that the ribs were soft and supported numerous hemorrhagic soft nodules, 0.5 to 1.5 cm. in size. These were slightly raised. The muscles were of a good red color and were moist. The thoracic fat measured 1 cm. and the abdominal fat 2 cm. in thickness.

The peritoneal cavity was free from fluid and adhesions. The diaphragm reached the level of the fifth rib on the left and the fourth rib on the right. The great omentum was large, moderately fatty and showed a few small red nodules, 3 mm. in diameter. These nodules were similar to other tumor nodules already described. The mesenteric fat was plentiful. There were numerous nodules in the mesentery which varied between a few millimeters and 1.5 cm. in diameter. It was presumed that they represented tumor growths in lymphoid tissue. Toward the periphery of the mesentery the nodules were small. In the midportion and the root of the mesentery the nodules were large, the largest being 1.5 cm. in diameter. These masses were composed of extremely soft friable dark red hemorrhagic tissue. A few appeared to be encapsulated, but in most the hemorrhagic tissue appeared to be invading the fat of the mesentery. Two nodules, 1 cm. each in diameter, were attached to the peritoneum lining the pelvis. These nodules projected above the surface but were not pedunculated. Like all others, they were soft, friable and hemorrhagic. A portion of one of these was pale and firm. It probably represented a more recent growth. The peritoneal surfaces were generally smooth, glistening and moist.

Each pleural cavity was free from fluid. The visceral pleura in each was smooth and glistening. The parietal pleura covering the ribs presented an irregular appearance because of underlying tumor nodules arising from the ribs. These nodules elevated the parietal pleura about 0.5 cm. in each instance. The presence of these dark red tumor masses caused great irregularity of the thoracic cage.

In the mediastinum a few anthracotic lymph nodes were present. There were no tumors similar to those previously described.

The pericardial cavity was free from adhesions. It contained the usual amount of clear yellowish fluid. The epicardial surfaces were smooth and glistening. There was somewhat less than the usual amount of subepicardial fat. The coronary arteries were slightly thickened but tortuous. The heart was soft but free from dilatation. The myocardium was of a good red color and showed no areas of softening or fibrosis. The endocardium was smooth throughout. The valve leaflets showed no essential changes. The foramen ovale was closed. The heart weighed 310 Gm. The circumferential measurements of the valves were as follows: tricuspid valve, 11 cm.; pulmonic valve, 7 cm.; mitral valve, 9.5 cm.; aortic valve, 8. The myocardium of the left ventricle measured 1.5 cm., that of the right ventricle, 0.5 cm.

In all portions of the aorta there was marked atherosclerosis.

The left lung weighed 265 Gm. The upper lobe was soft, gray and crepitant throughout. On section the tissue was dry and vesicular. Scattered diffusely throughout were a few bright red circumscribed areas which probably represented bleeding from the severed ends of blood vessels. The lower lobe was extremely small, grayish red, fleshy and noncrepitant. No definite tumor masses could be made out by palpation. On section the lung substance appeared grayish red and fleshy. Scattered here and there were a few slightly elevated hemorrhagic areas, which were but slightly firmer than the surrounding lung substance. These areas varied between a few millimeters and 1 cm. in diameter. They were poorly circumscribed and blended readily with the surrounding lung substance. Some of the larger areas appeared to be made up of collections of similar hemorrhagic areas. From gross examination it could not be said whether these reddish areas represented pneumonia or secondary tumor. The arterial tree was normal. There was no evidence of neoplasm in the bronchial tree.

The right lung weighed 260 Gm. The upper, middle and lower lobes were soft, gray and crepitant throughout. On palpation no nodules could be felt. On section numerous small hemorrhagic areas were seen scattered throughout all lobes. In the lower lobe these were fairly prominent and slightly firmer than in the others. As in the examination of the left lung, the question arose as to whether they represented neoplasm or foci of pneumonia. The arterial and bronchial trees were carefully examined and found normal.

The spleen weighed 180 Gm. It was free from adhesions. It was large, soft, dark red and flabby. When sectioned, it showed a soft, almost semifluid pulp which was finely mottled gray and red. The trabeculae were not increased in size. The follicles were difficult to differentiate. The pulp was homogeneous throughout, and there was no evidence of neoplasm.

The stomach was small, contracted and empty. The mucosa was pink, smooth and free from neoplasm. The lower portion of the esophagus was attached to the stomach and showed nothing of note. The small intestines were collapsed and empty. The mucosa was slightly congested in the same portions but not to a marked degree. A somewhat pedunculated firm nodule, 0.4 cm. in diameter, was found in the midportion of the ileum, beneath the mucosa. It appeared to

be a mass of lymphoid tissue. The appendix was not remarkable. The large intestine contained much fecal material, and the mucosa was slightly congested. No evidence of neoplasm was found in any portion of the gastrointestinal tract.

The pancreas was small and atrophic. There was some fatty infiltration. The pancreatic tissue proper was pale and firm.

The liver weighed 1,610 Gm. It was large. The surfaces were smooth and the edges sharp; the color was brownish red. Section revealed a finely mottled, reddish gray parenchyma. The finer markings were distinct. The tissue had a rather opaque appearance. The cut edge everted, and the parenchyma bulged to a slight extent.

The gallbladder measured 10 by 4 cm. It was thin walled and contained much thin green bile. There were no stones, and all the ducts were patent.

The right adrenal gland was not remarkable. The left adrenal gland was compressed but otherwise unchanged by a tumor mass 2 by 2 by 1 cm. which lay close to it. The tumor was composed of friable hemorrhagic tissue, which was sharply circumscribed.

The left kidney weighed 160 Gm. It was large, firm and free from congestion. The capsule stripped easily and displayed a relatively smooth pinkish gray surface which was free from scars. Section revealed a pale cortex which averaged 1 cm. in thickness. The cortical portions were sharply demarcated from the medullary portions. The large vessels showed only slight thickening. The pelvis was normal. The right kidney weighed 165 Gm. It was similar to its fellow.

The bladder was small, contracted and empty. The mucosa was rugose and was of a pink color. The walls of the bladder were thick.

The tubes and the ovaries showed the usual atrophic changes. Attached to the under surface of the left ovary there was a mass of hemorrhagic neoplastic tissue 1 cm. in diameter. It appeared to be growing outside of and compressing the ovary. The uterus was small and contained a single leiomyoma, 2 cm. in diameter, in the fundus. The cervix was small and partially occluded. The mucosa of the uterus presented several rather firm small polyps. One of these was cystic. These polyps were obviously benign.

The scalp was incised in the usual manner and reflected. The bones of the cranium will be described along with the skeleton in general. The calvarium was cut and removed. The dura was of normal thickness and did not bulge.

The brain weighed 1,300 Gm. The brain in situ was symmetric. The arachnoid vessels were slightly congested. The convolutions and the sulci were of normal proportions. After removal, the brain was symmetric. There was slight atherosclerosis of the large vessels at the base. The cerebellum and the medulla appeared normal. The attached portion of the cervical cord was not remarkable. There was no external evidence of tumor. The brain was set aside for hardening and future study.

The pituitary gland was small and congested but otherwise normal.

The linings of both ethmoid sinuses were easily removed. In the posterior portion of each there was a growth of dark red hemorrhagic tumor, measuring 0.5 cm. in diameter. These growths were symmetric and were attached to the outer surfaces of the base of the sella turcica, which contained neoplasm and which will be described later.

The greater portion of the spinal cord was removed by the abdominal route. The cord was normal as far as could be determined down to the level of the fourth thoracic vertebra. From this point downward the substance of the cord

was amorphous, soft and white. When the cord was sectioned, the substance of the softened cord could be squeezed from the surrounding arachnoid membranes. No structural pattern was visible in these softened portions. No sharp line of demarcation could be found between the softened and the unchanged portion of the cord. No cause for this softening could be found by gross examination.

Segments of the large lumbar nerves were taken for study.

The thyroid gland was small and symmetric. A small piece was taken for study.

In the calvarium there was a red hemorrhagic soft area, 1.5 cm. in diameter. It was located slightly to the left of the midline in the anterior portion of the left parietal bone. It extended completely through the thickness of the calvarium. A few similar areas, 0.3 cm. each in diameter, were observed in the most prominent portion of the right side of the frontal bone. After the brain was removed, the dura was stripped from the base of the skull. There was a softened hemorrhagic area in the bone; this formed the roof of the anterior portion of the left orbit. This area measured 1 cm. in diameter. Another softened hemorrhagic area was observed in the central portion of the left middle cerebral fossa. After the pituitary gland was removed, it was noted that almost the entire base of the sella turcica was soft, hemorrhagic and crumbly.

The sternum presented no projecting tumors, but a medial section showed that there was great softening of all portions of the sternum. The cortices of the bones were thinned out and soft. The cancellous portions were largely replaced by a soft hemorrhagic tissue. The sternum bent and fractured easily.

Every rib presented irregular tumefactions, 0.5 to 1.5 cm. in diameter. These swellings were raised to the extent of 0.5 cm. They were extremely numerous and in some instances were closely set. They were present in the anterior and the posterior portions of the ribs and were observed on the external as well as on the internal surfaces. Some of the tumors extended into the surrounding muscles. There were no ulcerations of the parietal pleura. The ribs were soft and fractured easily. Sections showed that the tumors replaced the bony structures as well as the marrow spaces. The tumors were soft, friable and hemorrhagic. All the rib marrow was extremely soft and red, probably owing to replacement by neoplasm.

The vertebral column was examined as far as possible. In all portions a replacement of the cancellous bone anl sometimes of the cortex by soft hemorrhagic tumor was observed. The neoplastic process was most marked in the lumbar segments but was distinctly visible as high as the third thoracic segment. In the lumbar region the vertebral segments were reduced to a mere soft red jelly. The interior vertebral disks were soft, apparently edematous and greatly swollen. Some of them measured 1.4 cm. in thickness.

Numerous sections of the right ilium were made. The bone marrow showed no changes as far as investigated.

The right femur was examined in its midpoint. After the muscles had been stripped away, the bone presented a mottled hemorrhagic appearance. It cut with some ease. The segment of the cortex was lifted off, and it was observed that the cortex was greatly thinned out owing to invasion by neoplasm similar to that described before. The marrow spaces contained large quantities of soft, almost jelly-like dark red tumor.

There was a pathologic fracture in the right humerus at the junction of the middle and the upper third. There was some palpable tumefaction at this point, and crepitus was noted. The site of fracture was examined. There was only

slight evidence of the formation of callus. The fractured ends of the bone were ragged and soft and showed marked neoplastic invasion. The cortical portions of the bone were thinned out and the marrow cavity contained soft red tumor.

The provisional anatomic diagnoses were: multiple myeloma involving the skull, the spine, the ribs, the sternum, the humerus and the femur; secondary myeloma of the abdominal lymph nodes; secondary myeloma of the lung (?); early bilateral bronchopneumonia; atelectasis of the lower lobe of the left lung; leiomyoma of the uterus; benign endometrial polyps; atherosclerosis of the aorta.

Examination of the Brain After Hardening in Formaldehyde Solution (Dr. G. H. Klinck Jr.).—The external appearance of the brain was similar to that of the organ when fresh. The brain was examined by making numerous parallel frontal sections. These sections revealed that the normal patterns of white and gray matter were present. There were no areas of softening or hemorrhage. The ventricles were of normal size, and their linings appeared smooth and glistening. Sections through the pons varolii, the cerebellar hemispheres and the medulla showed no remarkable changes.

Microscopic Examination.—Heart: The epicardium was not remarkable except for the fact that it contained a large quantity of fat. The branches of the coronary artery showed a moderate degree of thickening. The branches deep within the heart muscle were surrounded by an increased amount of fibrous connective tissue. The endocardium showed slight thickening in a few places. The fibers of the heart muscle were in general well preserved but in a few places they were being replaced by fibrous connective tissue. A moderate number of fibers of the heart muscle were much larger than normal.

Two poorly circumscribed collections of atypical cells were observed within the myocardium. These cells were generally round in outline, and many of them appeared to be plasma cells. A number of cells containing multiple nuclei were observed. It was believed that these cells were identical with those found in the tumors located in the other portions of the body.

Aorta: One section of the aorta showed a moderate degree of hyaline thickening of the intima. The media and the adventitia were not remarkable.

Lungs: Numerous sections of the lungs were studied. The pleural surfaces showed nothing worthy of note. Marked congestion of almost all the pulmonary vessels was observed. In many of the sections numerous air sacs were filled to capacity with large amounts of fibrin, polymorphonuclear leukocytes and mononuclear phagocytes. Occasional round cells also were present in the exudate. Many air sacs contained large amounts of finely granular acidophilic material, which was doubtless precipitated protein of edema fluid. All branches of the bronchial tree contained large amounts of degenerating inflammatory exudate. This exudate consisted of fibrin and debris. In some of the branches of the bronchial tree the exudate also contained large numbers of small round cells appearing to be lymphocytes. In some sections there was a moderate degree of fibrosis of the lung substance. Further examination failed to disclose the presence of any secondary tumor nodules.

Spleen: The capsule of the spleen was slightly thickened. The splenic follicles were few and small. The central portions of many of these follicles contained deposits of dense hyaline material. Some of the splenic sinuses were moderately congested; others were markedly congested. The pulp appeared unusually cellular. This appearance was due to the presence of enormous quantities of plasma cells. These cells much resembled the plasma cells found in the tumor nodules previously described. There were no localized growths of tumor cells.

Pancreas: In the pancreas a moderate degree of fatty infiltration was observed. There was a slightly increased amount of interacinar fibrous tissue. The acinar cells showed no unusual changes. The islet cells appeared normal, and the islets were normal in number. No secondary tumor masses were observed.

Liver: The liver cells were swollen and granular and lacked definite cell outline. The cells in the central portions of the lobules showed a moderate degree

Fig. 7 (case 3).—Photomicrograph of the myocardium, showing infiltration of mononuclear and multinuclear cells similar to tumor cells found elsewhere in the body.

of parenchymatous degeneration. Actual necrosis was not observed. All the sinuses of the liver were large and contained innumerable cells. In addition to erythrocytes and debris there were large numbers of round cells present. Many of these were definitely plasma cells; they resembled the cells found in the tumor nodules described elsewhere. In addition to these cells there were also numerous

rather small multinuclear giant cells. These cells were of the same type as those found in the secondary tumor masses previously described. No definite circumscribed collections of tumor cells were observed in any sections of the liver studied. A large number of lymphocytes were found in the periportal fibrous tissues. The significance of myeloma cells in the sinuses of the liver was not clear.

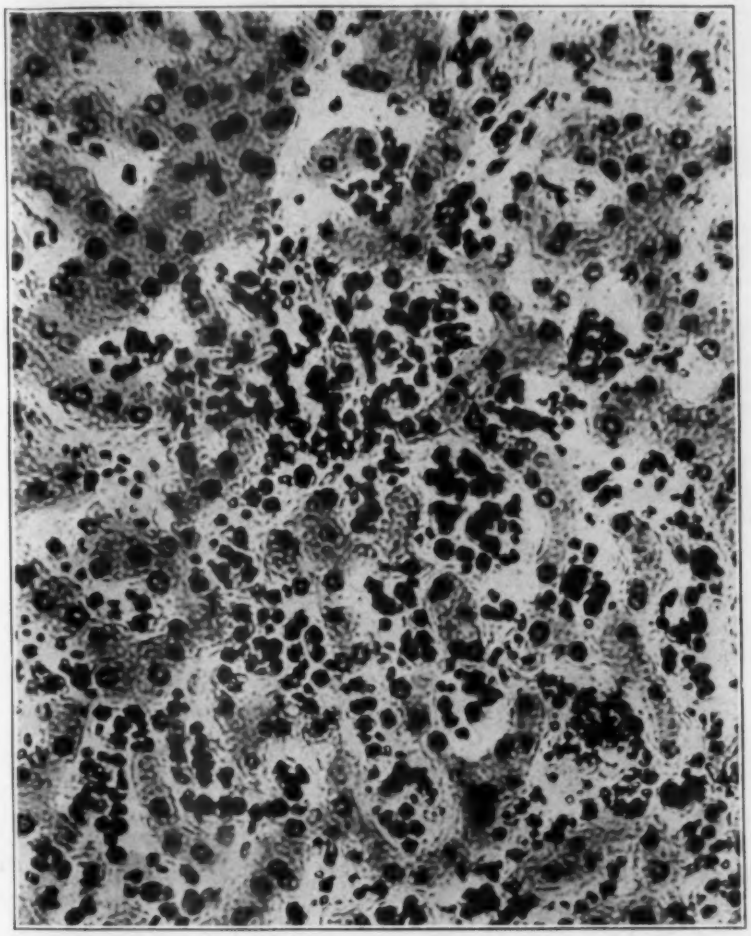

Fig. 8 (case 3).—Photomicrograph of a section of the liver. The sinusoids of the liver contained large numbers of tumor cells similar to those found elsewhere in the body. Many multinucleated cells are shown.

Adrenal Gland: A section of one adrenal gland showed no remarkable changes. Adjacent to the glandular tissue there was a large mass of secondary myeloma. This neoplastic tissue was identical with that already described.

Kidneys: The branches of the renal artery showed a moderate degree of thickening. This was most conspicuous in the large and the medium-sized

branches. Occasionally, hyalinized glomeruli were observed; other glomeruli were congested but showed no remarkable changes. There was marked swelling, cloudiness and granularity of the epithelium of the convoluted tubules. Many of these cells lacked definite cell outlines. Between some of the tubules there was an increased amount of fibrous tissue. No tumor cells were observed in any of the sections studied.

Bladder: Sections of the bladder showed that the mucosa was well preserved and that there was nothing unusual about the muscle coats.

Genitalia: A section of the uterus revealed the presence of a large endometrial polyp. The glands in this polyp were small, but the stroma was exceedingly dense. The stroma cells were oval and appeared to be of the normal type, but they were unusually numerous.

Ovary: The ovarian tissue was normal appearing. Attached to one pole of the ovary there was a mass of neoplasm. The tissue was loose in texture, exceedingly vascular and extremely hemorrhagic. The bulk of the tumor was composed of large numbers of round cells of the plasma cell type. A moderate number of tumor giant cells were also present.

Retroperitoneal Tumor Mass: In the periadrenal fat a large mass of secondary tumor was observed. This tumor tissue was extremely vascular and markedly congested. The bulk of the tumor consisted of large numbers of plasma cells and round cells which did not show the typical characteristics of plasma cells. In addition there were numbers of tumor giant cells containing between three and four nuclei. Little cytoplasm was observed in these cells.

Thyroid Gland: The acini were large and filled with colloid substance. The acinar cells were considerably flattened. The picture was that of a somewhat underactive gland.

Bone Marrow: Sections of the bone marrow from the vertebra, the sternum, the ribs, the femur and the skull were studied. In general, sections from the various portions showed essentially the same changes. Normal bone marrow was only occasionally recognizable; the bulk of the marrow was replaced by an overgrowth of cells characteristic of myeloma. The cell which appeared most frequently was a fairly typical plasma cell. This cell was large and had an ovoid or round nucleus in which the chromatin material was arranged in radiating bands like the spokes of a wheel. All of the nuclei contained nucleoli. The cytoplasm of these cells varied in amount and was generally clear. Numerous cells containing two or four nuclei were observed. These nuclei were generally similar to the ones occurring in the mononuclear cells. Another type of cell, somewhat smaller than the plasma cell, was observed; it was round or ovoid and had a rather dense nucleus and relatively little cytoplasm. Numerous transition forms between the two cell types were observed. In all instances the myeloma tissue was extremely vascular; the vessels were usually markedly congested, and large numbers of erythrocytes could be seen in the tissue spaces. There was relatively little supporting stroma in the tumor masses. It could be seen that the cortical portions of bone were being eroded by adjacent tumor. A section of rib showed that the myeloma tissue had extended completely through the cortex and was infiltrating the adjacent soft tissues.

Fractured Ends of Right Humerus: Sections from the fractured ends of the right humerus showed the presence of large amounts of myeloma tissue in bone and adjacent fat tissues. Attempt at repair of this was indicated by the presence of relatively small amounts of rather loose fibrous tissue containing large numbers of recently formed blood vessels. In all portions there was much hemorrhage.

Degenerating bits of bone could be seen near the site of the fracture. A small amount of recently formed bone was observed.

Intervertebral Disks: Sections of these disks revealed a vascular loose edematous fibrous connective tissue which showed signs of degeneration.

Brain: Sections of cerebral tissue showed that the vessels in the arachnoidal spaces had walls of normal thickness and were free from inflammatory reaction.

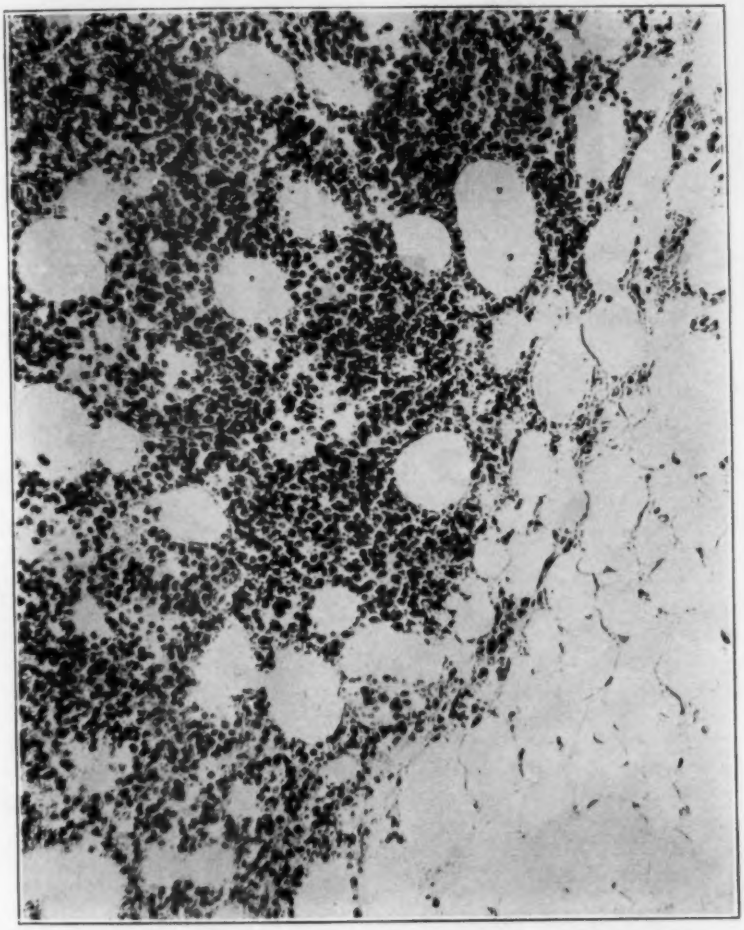

Fig. 9 (case 3).—Photomicrograph of a section of retroperitoneal fat, showing extensive infiltration of tumor cells. Mononuclear and multinuclear cells are shown invading the fat.

Sclerosis of the subarachnoidal tissues was present in a mild degree. The vessels in the brain tissue showed moderate congestion and dilatation of the perivascular lymph spaces. The cerebral substance proper showed nothing extraordinary. The choroid plexus was normal in appearance and showed few foci of calcification. No inflammatory reactions were observed in any portions of the brain studied.

Spinal Cord: Sections from the cervical portion of the spinal cord showed no unusual changes. Various sections from the softened portion of the cord revealed extensive degenerative changes. In almost all these sections the cord substance was reduced to a loose syncytial-like mass of degenerating nerve tissue containing a moderate number of mononuclear phagocytes filled with lipoid material. This condition obtained from the upper portions of the softened area down to the filum terminale. In these sections it was observed that the nerve trunks leaving the spinal cord also showed marked degenerative changes.

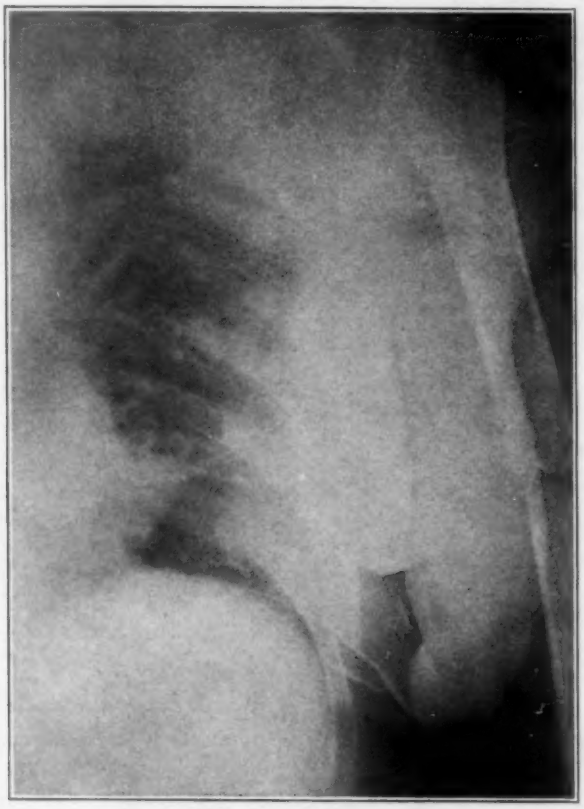

Fig. 10 (case 3).—Roentgenogram showing fracture in the right humerus; the fracture is in end to end contact, and there is a slight degree of angulation.

In a section taken from the lower portion of the spinal cord it was noted that copious hemorrhage had occurred. The tissues in and around the region of the hemorrhage contained many polymorphonuclear leukocytes. The hemorrhage apparently was old. No indication of the cause of the softening could be had from the sections studied or by gross examination. The larger vessels of the pia arachnoid showed moderate thickening of their walls.

Pituitary Gland: Section of the pituitary gland revealed no abnormalities.

Report of Roentgen Observations.—July 23, 1934: There was an increase of density in the lower articular portion of the body of the twelfth dorsal vertebra. The cartilage between this and the first lumbar vertebra was diminished in thickness. There were no arthritic changes in the tenth and eleventh dorsal or in any of the lumbar vertebrae. The sacroiliac joints and the hip joints appeared normal. The fifth lumbar vertebra was in normal relation to the sacrum.

August 27: The large bowel filled normally. Normal markings were visible throughout the course of the colon. There were no constrictions or filling defects. The esophagus was normal; the stomach was of the steer horn type and was

Fig. 11 (case 3).—Roentgenograms showing metastatic tumors in the shaft of the femur.

normal in size, shape and position. The outline of the stomach and the cap was normal. There were no defects suggesting ulceration or new growth. In six hours the stomach was empty. The barium sulfate was accumulated in the terminal portion of the ileum and in the ascending colon.

August 28: In twenty-four hours the barium sulfate filled the ascending, the transverse and the proximal half of the descending colon.

November 17: There was fracture through the middle of the shaft of the right humerus. There was evidence of fracture through the ninth rib on the right side.

November 19: After the application of a molded plaster splint, a fluoroscopic examination of the right arm disclosed the fracture in end to end contact. There was a slight degree of angulation.

Roentgenograms of the chest disclosed evidence of fracture of the sixth, seventh, ninth and tenth ribs on the left side of the chest. There was evidence of metastasis in the ribs on both sides of the chest.

There was evidence of thickening of the pleura on the left side toward the mediastinum about the apical portion of the lung; this may have been due to invasion by tumor or to effusion along the medial aspect of the lung. The eighth dorsal vertebra and the body of the fourth lumbar vertebra were partially collapsed.

There was evidence of metastatic tumor in the shaft of each femur and in the area just below the lesser trochanter in each femur. The growth was more advanced on the left than on the right side.

There was definite evidence of primary tumor. The more extensive changes in the left side of the chest suggested the possibility that the tumor might have been primary there.

September 27: To the left of the midline and just anterior to the coronal suture there was evidence of metastasis in the skull; this growth measured approximately 2 cm. in diameter. The sella turcica was normal in size and shape. There was no evidence suggestive of intracranial pressure.

Case 4.—N. D., a 24 year old Italian housewife, was admitted to the Albany Hospital on July 10, 1935 complaining of pain in the lumbar region which radiated to the thighs and around to the abdomen. She had not been well for six months, and in that period she had had pain in nearly all parts of the body, including severe frontal headaches and orbital pains.

On examination, she showed no physical signs, except some tenderness along the dorsal and the lumbar vertebrae and the right sacroiliac joint. Rectal examination revealed tenderness with erosion approximately 0.5 cm. in diameter on the internal aspect of the sphincter toward the left and posteriorly. She was well nourished and did not appear ill. On walking, however, her gait was striking; she did not lift her feet from the floor and appeared apprehensive. There was no movement in the lumbar region of the spine. There was no lymphadenopathy. The examination otherwise revealed no abnormalities.

An examination of the blood two days after admission gave results as follows: hemoglobin, 70 per cent; red blood cell count, 3,740,000; white blood cell count, 26,400 (one week later it was 7,850); polymorphonuclears, 72 per cent; lymphocytes, 20; myelocytes, 3. Blood cultures made on two occasions failed to yield growth.

On only one examination did the urine contain albumin (a trace), though numerous examinations were made.

On July 13, the urine was examined for Bence Jones protein, which was not present. On July 23, however, the protein was present.

A Wassermann test was negative.

On July 13, roentgen examination showed no evidence of metastatic tumor in the skull, the lungs or the ribs.

On August 2, roentgen examination brought to light evidence of destruction and collapse of the tenth dorsal vertebra; this suggested metastatic tumor. There was no evidence of metastatic tumor in the ribs or in the cervical vertebrae.

During her stay in the hospital up to August 21, inclusive, the patient's temperature ranged irregularly from 99 to 103 F. When she left the hospital her temperature was 100 F. The night before her discharge it was 103 F.

Apparently no blood pressure readings were taken.

A roentgen examination made before the patient left the hospital showed in addition to the observations already noted erosion of the third lumbar vertebra, of the right wing of the sacrum and of the left acetabulum.

A probable diagnosis of metastatic tumor was made. No primary lesion was found. Alcohol introduced intraspinally gave some relief from pain. High voltage roentgen therapy was instituted but stopped because of the extreme nausea and vomiting which followed each treatment.

On September 17, the patient reentered the hospital, having had a progressively downhill course during the few weeks away from the hospital. The pain had continued unabated. For about one week prior to admission she had become progressively short of breath, and her legs and ankles had become greatly swollen.

At the time of this admission there was little change in the results of physical examination, except for the swelling of the legs and the ankles. Numerous moist bubbling rales were heard at the bases of both lungs; the respirations were rapid and shallow.

The blood pressure was 80 systolic and 60 diastolic. The temperature was 98 F.; the pulse rate was 160; the respiratory rate was 48.

The urine showed a trace of albumin; otherwise it was normal.

The hemoglobin content had dropped to 52 per cent; the differential count was not indicative of any change in the blood.

On the fourth day after admission, the breathing became more rapid and labored and the pulse extremely rapid. The legs and the abdomen were tremendously edematous and tender to the touch. On several occasions death seemed imminent, but the patient rallied. Finally, the respirations became much more irregular, and the patient died within a few minutes.

The diagnosis made was possible multiple myeloma or secondary carcinoma.

Unfortunately, no chemical examinations were made.

Report of Roentgen Observations.—July 13, 1935: There was no roentgen evidence of metastatic tumor in the skull, the lungs or the ribs.

August 2: There was evidence of destruction and collapse of the tenth dorsal vertebra, suggesting metastatic tumor. There was no evidence of metastatic tumor in the cervical vertebrae. Further examination showed erosion of the third lumbar vertebra, of the right wing of the sacrum and of the left acetabulum.

Autopsy.—The body was that of a well developed and well nourished obese Italian girl, 24 years of age. The length of the body was 134 cm. Rigor mortis was not present. There was livor mortis of the dependent portions. There was marked pitting edema of both lower extremities, and there was moderate edema of the hands and the flanks. The surfaces of the skin were smooth and moist and showed no eruption. The hair was long and black. The ears and the nose were normal. The pupils were equal, round and regular and were mid-dilated, measuring 0.4 cm. in diameter. Two large vaccination scars were present on the left upper arm. The abdomen was large and rotund, and the skin showed many striae.

The panniculus adiposus measured 2 cm. in thickness. The subcutaneous tissues were moderately edematous, but no fluid was present in the peritoneal space itself. The mesothelial surfaces were smooth, moist and glistening. No adhesions were present. The diaphragm was at the level of the seventh rib on the left and at the level of the sixth interspace on the right. The inferior vena cava was thrombosed.

Inasmuch as the autopsy incision was limited to the abdomen, the heart and the lungs were removed through the diaphragm; accurate inspection of these cavi-

ties was therefore not possible. However, no excessive fluid was observed, and the surfaces appeared smooth, pale and glistening. No adhesions could be palpated.

The heart weighed 220 Gm. It appeared small for the weight of the patient. The myocardium was meaty red and flabby. It measured 0.5 cm. in thickness in the left ventricle and 0.2 in the right. The coronary arteries disclosed nothing of note. The left ventricle showed flattening of the trabeculae carneae and appeared relatively enlarged. However, the valve rings had normal circumferences: the tricuspid, 10 cm.; the pulmonic, 5 cm.; the mitral, 9 cm.; the aortic, 5 cm. The endocardium of the valve leaflets and throughout the chambers of the heart showed nothing of note.

In the aorta there were no noteworthy changes. In places the vessel was rather small, apparently from compression by adjacent tumor tissue.

The right lung weighed 280 Gm. and the left 250 Gm. Each was pinkish gray and spongy. On the costal surface of the middle lobe of the right lung was a firm whitish nodule, 3 cm. in diameter and extending 0.8 cm. into the lung substance. On section this tissue was firm and whitish and appeared highly cellular. It was not encapsulated. The remainder of the lung showed nothing of note.

The left lung, like the right, had smooth pleural surfaces. It contained a single elongated spoon-shaped deep reddish raised focus, 11 by 1 cm. in size and extending 1 cm. into the lung substance. Its cross section was roughly wedge shaped, typical of a hemorrhagic infarct. The remainder of the lung was pinkish, spongy and crepitant throughout. There was no evidence of a pneumonic process.

The spleen weighed 230 Gm. It was firm in consistency, and its capsule was smooth and deep purple. On section the pulp was solid and deep purplish red. The lymphoid follicles were not prominent.

The esophagus and the stomach showed nothing of note. Grossly, the small intestine, the appendix and the large intestine were normal.

The pancreas showed nothing of note.

The liver was enlarged and weighed 2,100 Gm. It was yellowish brown and mottled and on section presented yellow greasy speckled cut surfaces. Serial sections yielded no evidence of tumor nodules in the parenchyma.

The gallbladder was thin walled and contained about 40 cc. of thick yellow bile. The ducts were patent.

The adrenal glands showed nothing of note.

The right kidney weighed 290 Gm. It was buried in a large mass of fat which was infiltrated with white neoplastic tissue that was present retroperitoneally along the margin of the spinal column. On section the perinephric fat was seen to be invaded by white cellular tumor tissue and was adherent to the capsule of the kidney over its lower three quarters. About a dozen small round white cellular nodules were present in the renal cortex itself. These nodules averaged 0.3 cm. in diameter. The pelvis was dilated, and its walls had the appearance of ground glass. The cortex itself was pale and yellowish white with many yellowish lines which radiated from the pelvis outward. The medulla was likewise pale, and the corticomedullary junction was indistinct. The ureter was embedded in a mass of fat and tumor tissue. A fine probe was passed through its lumen only with considerable force.

The left kidney weighed 240 Gm. It was pale and flabby. Its capsule was smooth and stripped with ease. On section the cortex and the medulla were pale yellowish with whitish radiating streaks similar to those in the right kidney. The corticomedullary junction was indistinct. Three small tumor nodules similar

to those in the right kidney were present in the cortex. The pelvis was slightly distended. The ureter was patent.

The bladder showed nothing of note. A small amount of clear yellow urine was present.

The uterus, the tubes and the ovaries were not remarkable. The veins of the broad ligament on the right side were thrombosed.

Practically all of the retroperitoneal lymph nodes situated to the right of the spinal column as well as many on the left side and in the pelvis were replaced by soft friable pinkish white neoplastic tissue. Except for the tumor growth about the right kidney, all of the tumor was in lymph nodes or in bone, as will be described later. In some places, small hemorrhages had taken place in the neoplastic nodes. The tumor tissue was so soft that it crumbled easily and seemed to be almost devoid of stroma.

The bodies of the tenth thoracic and third lumbar vertebrae were practically destroyed by a friable infiltrating neoplasm which grew apparently from within the bone, involving first the bone marrow and extending peripherally to invade and erode the cortical portions of these bones. The sacrum just to the right of the midline was also destroyed and eroded by tumor tissue. In all these places the neoplastic tissue could be scooped out readily. It was grayish pink, soft, moist and often hemorrhagic and contained almost no detectable stroma.

Grossly, the nature of the neoplasm was difficult to determine. Multiple myeloma immediately suggested itself, especially since Bence Jones protein was said to have been found in the urine during life. However, multiple myeloma rarely metastasizes to viscera. Primary lymphoblastoma of the retroperitoneal lymph nodes with metastases to bone and to other organs was a likely possibility. Perhaps the tumor was an acute form of Hodgkin's disease. From gross examination alone we were inclined to favor the diagnosis of primary lymphoblastoma of the retroperitoneal lymph nodes, possibly acute Hodgkin's disease.

Microscopic Examination.—Heart: The muscle cells of the left ventricle of the heart were normal in size. Many of them were hydropic, and here and there were small vacuoles which apparently had contained fat. These degenerative changes were most pronounced in the subendocardial regions. Several small foci of necrosis of the myocardial cells also were found. In these regions the affected cells showed a loss of the normal striations and granulation of the cytoplasm with a tendency toward acidophilic staining. Endothelial leukocytes were present in the subendocardial regions. The epicardium and endocardium showed no noteworthy histologic changes.

Aorta: The aorta, especially in the abdominal portion, showed nothing of note histologically except moderate hypoplasia. The lumen of the vessel was slightly less than 1 cm. in diameter. In the adventitia of the vessel there was extensive local infiltration of a rapidly growing malignant tumor composed of small and large irregularly round or oval discrete undifferentiated cells, many of which were multinucleated. The growth did not affect the media or the intima of the vessel. The tumor was apparently an extension into the adventitia from adjacent retroperitoneal lymph nodes. The neoplasm will be described at more length.

Lungs: Sections from the right lung showed moderately edematous vesicular tissue. In one section a large metastatic neoplastic mass was present. Like that already described, this tumor consisted of great numbers of discrete round or oval cells, often multinucleated, with little stroma, and large numbers of thin-walled congested blood vessels were present in it and probably accounted for the absence

of foci of necrosis. Often the cells appeared to be confined in narrow, elongated spaces surrounded by thin delicate strands of connective tissue. Here and there slight hemorrhages had recently occurred. In these regions phagocytic endothelial leukocytes filled with blood pigment (hemosiderin) were present in considerable numbers. A single hyaline scar was observed in the tumor tissue. Adjacent to it a fairly large branch of a pulmonary artery was thrombosed, and

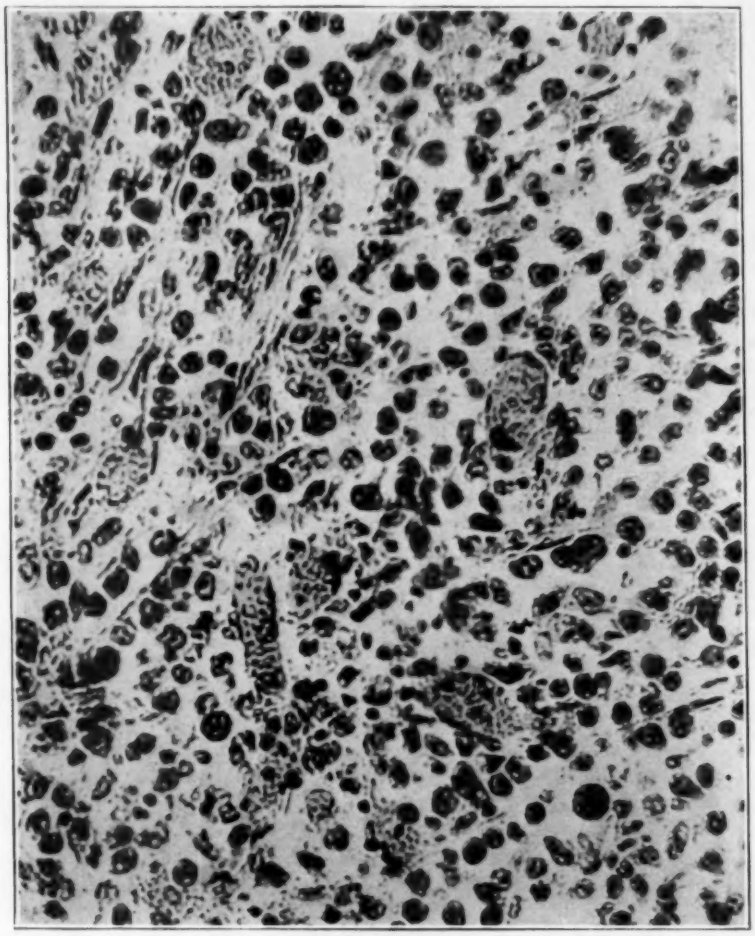

Fig. 12 (case 4).—The patient had secondary tumor in the lung. The photomicrograph shows a portion of the tumor that has completely destroyed the pulmonary parenchyma. Several multinucleated cells are shown.

the thrombus was undergoing organization. The scar appeared to be a small healing infarct.

In some sites the neoplastic cells infiltrated the pulmonary stroma rather widely, especially in the interlobar septums. In other places the growth was present with blood or lymph vessels. It was believed that the tumor reached the lung by means

of the blood and that further growth was by direct extension through tissue spaces or by way of the lymphatics.

Adjacent to the new growth the pulmonary tissues were edematous, and the alveoli contained many endothelial leukocytes, some of which were phagocytic. In some of the alveoli masses of fibrin also were present, but there was no evidence

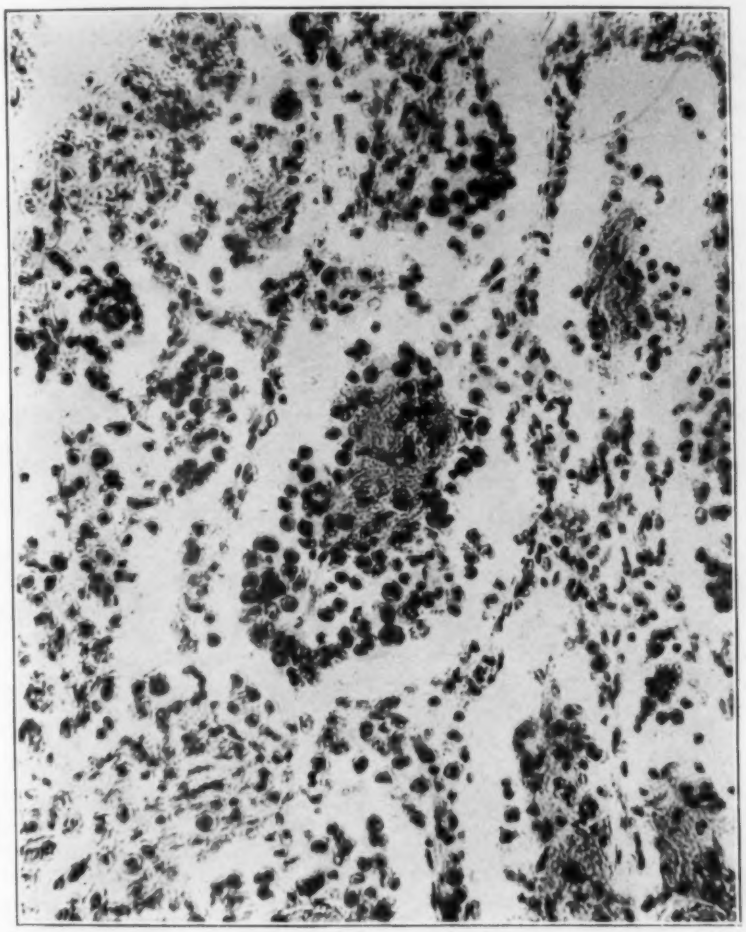

Fig. 13 (case 4).—Several alveoli containing masses of monocytes and fibrin are shown. These alveoli are adjacent to a large mass of secondary neoplasm, and the cells in the alveoli are considered to be neoplastic. Multinucleated cells are shown.

of an infectious inflammatory process. The reaction was apparently secondary to the infiltration by the tumor of the pulmonary tissue.

A section from a lymph node in the region of the hilus of the right lung showed extensive infiltration by the same type of tumor as that in the right lung.

The neoplasm appeared definitely to be a metastasis and not a primary growth. The same histologic features which characterized the metastasis in the right lung were found in this tumor.

Sections from the left lung showed congested, slightly edematous vesicular tissue. In two of the sections recent typical hemorrhagic infarcts were present. At the lower edge of one of these, a large thrombosed branch of a pulmonary artery was observed. This was undoubtedly the cause of the infarct. In the infarcted regions, the pulmonary tissues were undergoing degeneration, and large numbers of red blood cells and much fibrin and serum were present in the alveoli. The edges of the infarcts were fairly sharp. The adjacent vesicular tissue was edematous; the more remote tissues showed no noteworthy changes. No neoplasm was found in the sections studied.

Spleen: The spleen was congested. Occasional areas in which slight hemorrhages into the pulp had taken place were observed. There was no histologic evidence of tumor metastasis in the sections studied.

Pancreas: In general, the acinar tissue in the pancreas was histologically normal and was well preserved. In several small foci the structural pattern of the pancreas was destroyed by the infiltration of a metastatic neoplasm which resembled the growths already described. The malignant cells infiltrated the interacinar stroma and compressed or destroyed the acini and islets of Langerhans which were in the affected region. The islands of Langerhans were abundant and appeared well preserved. Many of these structures were hypertrophied, being from two to four times the normal size. The island cells showed no abnormal changes.

Liver: The liver was the seat of marked fatty degeneration; practically all the parenchymal cells, especially those in the central portions of the lobules, contained small and large fat vacuoles. In some places, especially in the subcapsular regions, there was evidence of early acute necrosis of small groups of hepatic cells. In general these foci were in the peripheral portions of the lobules, and in practically all of the periportal spaces polymorphonuclear leukocytes were abundant. The liver was thus the seat of marked fatty degeneration as well as acute cholangitis with acute focal necrosis of parenchymal cells in the peripheral portions of the lobules. There was no evidence of metastatic neoplasm in the liver.

Adrenal Glands: The adrenal glands showed nothing of note histologically.

Kidneys: Sections from the kidneys showed two distinct types of lesions: first, typical small unencapsulated metastatic tumors similar to those described; second, acute inflammatory lesions which involved practically all of the convoluted tubules—early acute tubular nephritis. In general the glomeruli showed little of note aside from acute congestion. The convoluted tubules, however, as well as the renal stroma about them, were infiltrated with great numbers of polymorphonuclear leukocytes and occasional strands of fibrin. Fluid was not abundant. Often the leukocytes were in the process of removing necrotic tubular epithelial cells. Henle's loop and the collecting tubules were not inflamed, but in some of them small masses of purulent exudate, presumably from the convoluted tubules, were present. The lesion was considered to be acute tubular nephritis of toxic origin.

The tumor metastases were small, consisted of large accumulations of atypical cells similar to those found in other organs and completely destroyed the parenchyma of the kidney wherever they were present. The cells were separate and discrete, appeared round or oval with lobulated, irregular nuclei and had little stroma. Mitoses were frequently seen.

Genitalia: The myometrium and the endometrium showed nothing of note. The endocervix contained many large retention (nabothian) cysts but was otherwise not remarkable. The ovaries were normal. Sections from veins in the broad ligament showed them to be acutely thrombosed.

Retroperitoneal Lymph Nodes: Lymph nodes from about the aorta, as previously noted, as well as about the inferior vena cava and in other portions of the retro-

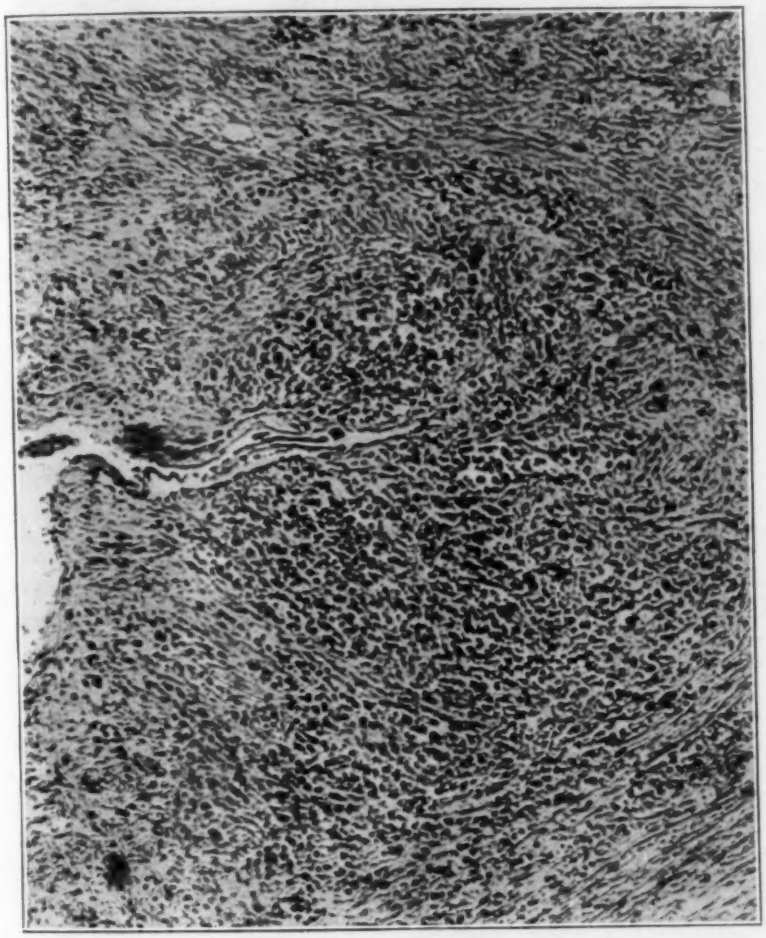

Fig. 14 (case 4).—Heavy infiltration of tumor cells into the periaortic tissues.

peritoneal tissues, were the seat of a rapidly growing highly invasive neoplasm. The cells varied considerably in size and shape, but tended to form no recognizable structures. They were undifferentiated and primitive. Mitotic figures were present in large numbers. The most typical cells were large and irregular and had deeply pigmented lobulated nuclei. Often the nuclei were multiple. These cells resembled somewhat megakaryocytes of the bone marrow. If this is true, the tumor may have been an acute form of Hodgkin's disease, although the tendency to fibrosis was slight.

However, other varieties of cells recalled primitive bone marrow cells and thus suggested myeloma of the myeloid type.

Sections from the vena cava showed that the tumor had penetrated the vessel wall from without and had led to the formation of a thrombus which completely filled the lumen.

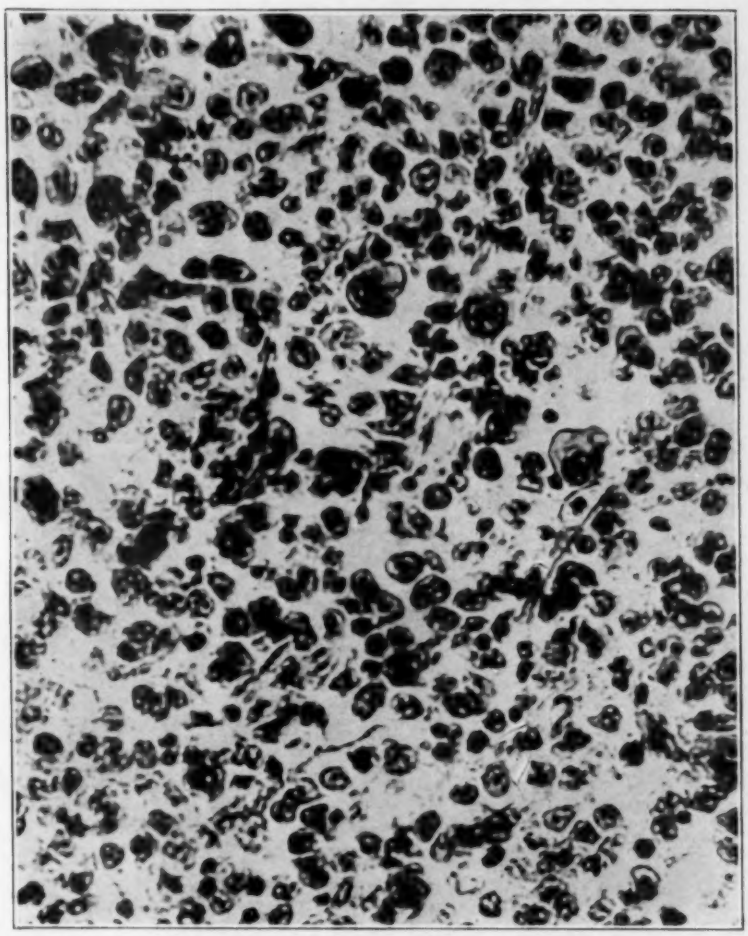

Fig. 15 (case 4).—Photomicrograph showing the structure of a lymph node replaced by tumor cells that vary in size and shape and do not tend to form recognizable structures. Many multinucleated cells are shown.

Bone Marrow: Sections from the marrow of the right side of the sacrum and from that of the bodies of the tenth dorsal and the third and fourth lumbar vertebrae all showed neoplasm of the same type as that already described. Foci of necrosis were present, but even though the fibrous stroma was fairly abundant, there were no large foci of sclerosis. The neoplastic cells, although they varied morphologically like those in the lymph node, appeared to be of bone marrow origin.

Summary.—In this case the anomaly consisted of a rapidly growing malignant tumor of the retroperitoneal lymph nodes and of the bone marrow of the sacrum and several vertebral bodies. Histologically the tumor was composed of highly undifferentiated cells believed to have their origin in the bone marrow. In our opinion, therefore, the neoplasm was multiple myeloma of the myeloid type.

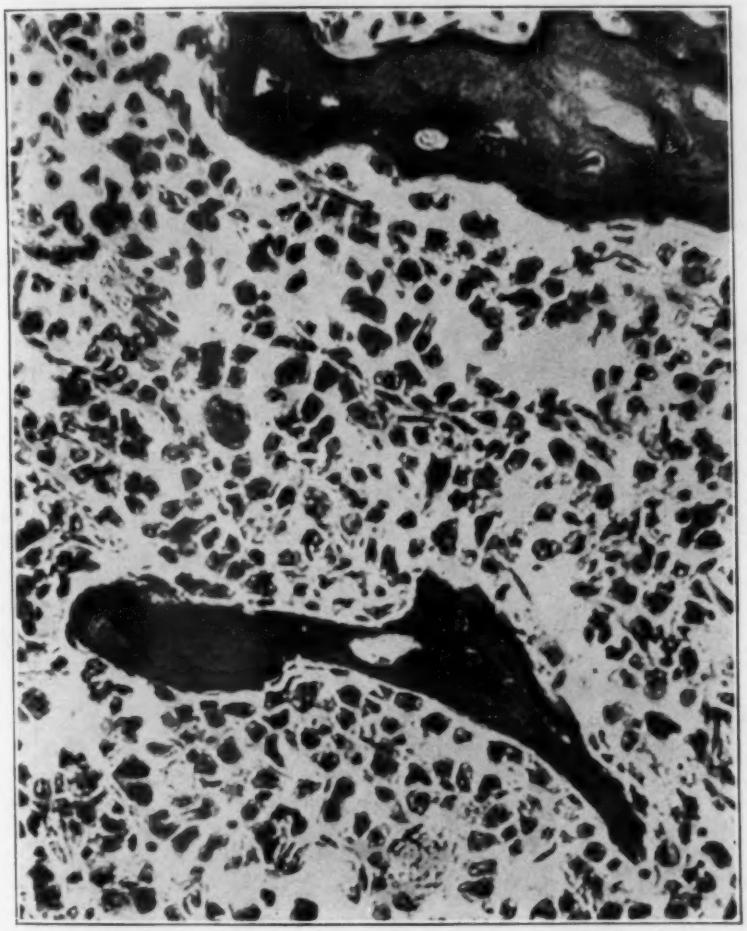

Fig. 16 (case 4).—Photomicrograph of vertebral marrow. The marrow cells are largely replaced by tumor cells. Several multinuclear tumor cells are shown.

If Hodgkin's disease is considered a primary tumor of the bone marrow with the megakaryocyte as the cell of origin, it is not possible to exclude it as a possible diagnosis. Dr. E. M. Medlar of Mount McGregor, N. Y., expressed the belief that the tumor was characteristic of acute Hodgkin's disease. Dr. F. Parker Jr. of Boston said that he "felt pretty sure" that the diagnosis was acute Hodgkin's disease. Dr. F. B. Mallory of Boston did not wish to commit himself.

TABLE 9.—*Data on the Patient in Case 5*

Date	Wassermann Tests	Blood Pressure, Mm. of Mercury	Blood Counts: Hemoglobin, per Cent	Red Blood Cells	Color Index	White Blood Cells	Differential: Polymorphonuclears	Differential: Lymphocytes	Differential: Myelocytes	Differential: Undetermined	Blood Chemistry: Nonprotein Nitrogen, Mg. per 100 Cc.	Blood Chemistry: Sugar, Mg. per 100 Cc.	Blood Chemistry: Icteric Index	Blood Chemistry: Carbon Dioxide-Combining Power, Volumes per Cent	Urine: Specific Gravity	Urine: Albumin	Additional Observations
2/ 6/32	..	.....	52	3,080,000	0.73	3,600	43	47	2	8	..	..	..	..	..	..	
4/ 4/32	..	110/68	..	.....	....	.....	..	..	..	..	..	..	..	..	..	—	Urine contained casts
4/10/32	..	110/70	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	
4/17/32	..	112/70	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	
6/22/32	..	100/40	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	
7/13/32	..	125/60	37	2,230,000	....	3,800	..	..	..	..	..	..	..	..	..	..	
8/ 3/32	..	110/60	38	2,450,000	....	.....	..	..	..	..	..	..	..	..	..	..	
8/10/32	..	118/55	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	
8/14/32	..	140/60	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	
9/ 3/32	..	.....	35	1,740,000	0.9	10,000	72	28	1	2	35	..	..	..	..	..	
9/ 4/32	..	.....	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	Roentgen examination showed that the sella turcica was normal in size; the posterior clinoid process was not well visualized
9/ 5/32	..	.....	..	.....	....	.....	..	..	..	..	37.4	..	3.125	38	1.015	+	Bence Jones protein was not present; urine contained many granular and hyaline casts
9/ 7/32	—	.....	..	.....	....	.....	..	..	..	..	..	105	..	..	..	..	Culture of the blood yielded no growth
9/22/32	..	.....	..	.....	....	.....	..	..	..	..	..	..	..	..	..	..	Culture of the blood yielded no growth

Dr. James Ewing and Dr. Fred W. Stewart of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, felt that this was a case of myeloma of the myeloid series. They stated further that "it is difficult to assign an origin in these typical cases, that one can't feel sure the erythroblastic origin is out of the picture. The giant cells look like abortive megakaryocytes."

Despite what appeared to be real differences of opinion, therefore, the general opinion concerning the tumor was that it was of bone marrow origin, regardless of the name used in diagnosis. The neoplasm was definitely not primary in the lymph nodes, and the gross diagnosis of lymphoblastoma had to be set aside.

Anatomic Diagnoses.—The final diagnoses were: multiple myeloma of the myeloid type of the third and fourth lumbar and tenth thoracic vertebrae and of the sacrum with metastases to the retroperitoneal lymph nodes, the inferior vena cava, the pancreas, the kidneys and the right lung; marked erosion of the tenth thoracic and third and fourth lumbar vertebrae and of the sacrum; thrombosis of the inferior vena cava and of the iliac, uterine and pulmonary veins; hemorrhagic infarcts of the lungs; acute focal necrosis of the myocardium; acute bilateral nephritis of the tubules; stricture of the right ureter; right hydronephrosis; fatty degeneration of the heart and the liver; hypoplasia of the aorta.

Case 5.—E. G., a 60 year old painter, was admitted to the Albany Hospital in moribund condition on Sept. 2, 1932. During the previous eighteen months he had been seen in the outpatient department a great many times and had been treated for a large variety of complaints, including chronic cough, weakness of the legs, dyspnea on exertion, blurring of vision and frontal headache. In February 1932 he had been admitted to the hospital because of increasing weakness, cough and brownish discoloration of the skin and the mucous membranes. At that time an excised portion of skin gave a negative reaction when tested for iron and showed the presence of melanin. After three weeks he was discharged with instructions to adhere to a high caloric diet and to rest as much as possible. A diagnosis of possible Addison's disease had been made. He was again followed in the outpatient department but was observed to be going gradually downhill. The weakness of the calves of his legs continued and grew more marked; at times he suffered epistaxis of considerable severity. Late in August his symptoms became much more marked; the headaches increased in severity and were accompanied by vomiting and dizziness. In the week before admission he became disoriented, and three days before entering the hospital he lapsed into a semicomatose state.

At the time of admission the patient was too weak to respond to questioning. There was marked bronzing of the skin, particularly of the face and the neck. The pupils reacted to light and in accommodation. The teeth were missing. The throat was somewhat injected. There were small pigmented areas on the hard palate. No enlarged lymph nodes were present. Examination of the heart revealed nothing unusual. The lungs were essentially clear. The abdomen and the extremities were not remarkable except for the pigmentation.

The patient never rallied from the semicomatose state. He was given dextrose intravenously. A blood transfusion was contemplated but not carried out because no satisfactory donors were available, the patient's serum agglutinating even his own cells. Two hours after admission he died.

Gross examination of the bone marrow at autopsy showed that the marrow of the ribs had been replaced by a white gelatinous friable material, the bulk of which was far greater than the normal bulk of the marrow content in these bones. The increased amount of this substance had apparently caused thinning of the bony cortex of the rib and had led to weakening of the structures. The ribs were

TABLE 10.—*Summary of F* *es of Multiple*

Case and Patient	Sex and Age	Presenting Symptom	Blood Pressure	Blood														Urine
				Hemoglobin, per Cent		Red Cell Count, Millions *		White Cell Count		Differential Count †						Bence Jones Protein		
										Polymorphonuclear Leukocytes, per Cent		Lymphocytes, per Cent		Myelocytes, per Cent				
				Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Examinations	Times Present	
Case 1 D. A.	M 57	Pain in back, right side of chest and shoulders	See table 3	95	72	5.69	3.50	10,000	3,950	84	69	34	12	7.5	3	28	12	‡
Case 2 R. H.	M 44	Lump in right groin	See table 7	103	75	5.35	4.15	15,200	9,200	82	63	28	13	5	4	3	0	
Case 3 H. H.	F 62	Pain in lower part of the back	See table 8	101	63	5.07	3.20	10,020	4,800	68	62	35	20	10	2	3	2	
Case 4 N. D.	F 24	Pain in lower part of the back radiating about hips and abdomen	80/60	70	52	3.74	No other count	26,400	7,850	72	72	20	20	3	3	2	1	
Case 5 E. G.	M 60	Generalized "bone pain," sharpest in midportion of the back	See table 9	52	38	3.68	1.74	10,000	3,000	72	43	47	28	2	1	1	0	

* No nucleated red cells were noted in any of the cases.

† In none of the cases were the basophilic or eosinophilic counts abnormal.

‡ At no time was Bence Jones protein found, and depending on the biopsy alone, we made chemical examinations. In re spect it appears that it would have been better to perform the routine chemical examinations of the blood.

Minimum	Bence Jones Protein: Examinations	Bence Jones Protein: Times Present	Urine	Kidney Changes (Observed at Autopsy)	Locations of Bone Lesions (Ascertained by Roentgen Examination)	Locations of Extraskeletal Involvement	Spontaneous Fracture	Diagnoses
3	28	12	…rely a trace of …bumin; finely …anular casts …out half the …me; occasionally …yaline cast	A few small subcapsular scars consisting of dense fibrous tissue infiltrated by various numbers of lymphocytes. Renal tissues in general, glomeruli, vascular system and renal pelves not unusual	Vertebrae, ribs, skull (including ramus of each mandible), clavicles, humeri, scapulas, radiuses, ulnas, femurs; generalized atrophic changes in bones of hands but no evidence of tumor	None	Present in rib	Primary diagnosis of hyperparathyroidism after roentgen examination; diagnosis changed after chemical examination and further roentgen study
4	3	0	…xorbitant …mounts of albu…in almost con…antly (patient …ated that his …ysician had …own this for the …st five years …t in absence of …sts paid little …ttention to it); …yaline casts on …l but one exami…ation in hospital	Capsules, normal thickness. Cortices, scattered foci of sclerosis with lymphocytic infiltration here and there. Glomerular capillaries, congested; many proliferated; many completely changed into masses of dense hyaline connective tissue; fibrosis of Bowman's capsule. Tubules, both postmortem and parenchymatous degeneration of epithelial cells in both cortical and medullary portions; many cells desquamated and lying free in lumens; small hyaline casts in many collecting tubules. Connective tissue stroma throughout kidneys increased, loose and edematous. Large blood vessels, slightly thickened internal coats. The renal changes were those of mild chronic vascular nephritis	Pubic bone, skull and seventh rib	Prostate gland and perprostatic tissue (by direct invasion)	Present in pubic bone	Constant diagnosis of general carcinomatosis, based on mass found in pelvis and on biopsy of tumor in forehead which yielded diagnosis of metastatic epithelial tumor ‡
2	3	2	…equent exam…ations: a trace …albumin once; …arge amount …ce, with a trace …sugar; micro…opic observa…ns always …gative	Branches of renal artery, moderate degree of thickening. Glomeruli, occasionally hyalinized. Convoluted tubules, marked swelling, cloudiness and granularity of the epithelium; many of these cells without definite cell outlines; between some of the tubules, increased amount of fibrous tissue	Humerus, ribs, vertebrae, skull, femurs	Heart, spleen, liver (?), periovarian tissue and periadrenal fat	Present in humerus and rib	Patient admitted three times; first diagnosis, flatfoot; second, possible metastatic carcinoma; third (after finding Bence Jones protein), possible multiple myeloma
3	2	1	…equent exam…ations: a trace …albumin once; …roscopic obser…tions always …gative	Two types of lesions: (1) typical small unencapsulated metastatic tumors similar to those described elsewhere; (2) an acute inflammatory lesion involving all convoluted tubules—early acute tubular nephritis. The tumor metastases consisted of large accumulations of atypical cells similar to those formed in other organs, which completely destroyed parenchyma of kidneys wherever they were present. The cells were separate and discrete, appeared round or oval with lobulated irregular nuclei and had little stroma. Mitoses were frequent	Vertebrae, sacrum and acetabulum	Lungs, periaortic tissue, retroperitoneal lymph glands, mediastinal lymph glands, pancreas, right kidney	Absent	Tentative diagnosis of possible myeloma or secondary carcinoma
1	1	0	…trace of albu…n at times; …ny granular and …yaline casts once	Kidney essentially normal	No rentgenograms made	Heart and spleen	No roentgenograms made	Possible Addison's disease or secondary carcinoma

…aminations. In m…

easily broken between the fingers. Examination of several ribs was convincing evidence that all of them were so affected.

The anatomic diagnosis was: cutaneous melanosis with old cerebral hemorrhage and questionable tumor of the bone marrow.

Microscopic Examination (Dr. Victor Jacobsen).—Heart: There was marked edema of epicardial fat. At the base of the left ventricle there was a coarse interstitial fibrosis with a few plasma cells and monocytes in the stroma. Muscle fibers showed hydrops and a normal amount of yellowish perinuclear pigment.

Spleen: In the spleen there was much hemosiderin both free and in phagocytes. Some phagocytes contained erythrocytes. Beneath the capsule was a zone in which there were many cells resembling somewhat the predominant cell in the vertebral and rib marrow.

Bone Marrow: The vertebral and the ilial marrow had been replaced by a cellular neoplasm. The type cell had some resemblance to the plasma cell but with variations; often it looked much like an erythroblast. Typical plasma cells were present in small numbers. Most of the cells were arranged in long narrow cords, separated by a delicate stroma, in which blood channels were inconspicuous. Invasion of the bone marrow by fat occurred. The bone cortex was thinned out, but there was no evidence of bone erosion or circumscribed marrow tumor. Mitoses were rare. The condition seemed to be a rare type of an essentially plasma cell tumor, a diffuse myelomatosis. The femoral marrow showed the picture of severe secondary anemia but with scattered cells of the same appearance as those in the vertebrae.

The microscopic diagnosis confirmed the diagnosis made after the gross examination. In addition, the following observations were made: subdural hemorrhage; chronic leptomeningitis; granular ependymitis; congenital asymmetry of the cerebrum; unilateral degeneration of the pyramidal tract; diffuse myelomatosis.

SUMMARY AND CONCLUSIONS

There were definite evidences of metastasis in 3 cases, including metastasis to the lung in 1 case.

There was widespread direct extension of the disease in case 2; in case 5, there was no evidence of metastasis or of direct extension.

In 3 of the 5 cases, Bence Jones protein was present in the urine.

The urinary findings were inconstant.

Roentgenograms must be examined skilfully.

In 4 of the 5 cases, pain in the back was the presenting symptom.

Though low blood pressure was present in 2 of our cases, it should not be considered as a pathognomonic sign.

Errors in diagnosis, as demonstrated by our cases, may sometimes be avoided by consistent determinations of the chemical composition of the blood.

All patients with pain in the back, especially those in the sixth decade of life, should be looked on with the idea that multiple myeloma may be present. This is especially true in those cases in which no injuries or only minor injuries appear in the history.

The cases reported are from the services of Drs. T. Ordway, A. W. Elting and J. L. Donhauser.

PHYSIOLOGIC BEHAVIOR OF THE HUMAN APPENDIX AND THE PROBLEM OF APPENDICITIS

REACTION OF THE APPENDIX TO DRUGS

CLARENCE DENNIS, M.D.
MINNEAPOLIS

PART 1. INTRODUCTION

I. PURPOSE OF THIS STUDY

Although a host of theories as to the etiology of acute appendicitis has been offered, many with strong supporting evidence, the disease has not been proved capable of experimental production either in man or in related species except by the obstructive mechanism.[1]

By longitudinal section of 91 surgically removed appendixes fixed in solution of formaldehyde, Wangensteen and Bowers[2] found all the gangrenous specimens to show obstruction of the lumen, but in only 72 per cent of 43 cases of acute suppurative appendicitis was obstruction demonstrable by this method, leaving 28 per cent of the group, or 12 cases, in which no obstruction could be demonstrated.

Through the studies reported in this paper it has been shown that a functional factor exists which may reasonably explain the absence of organic obstruction in some cases. Experiments will be outlined which have approached the nature of this functional factor from several angles and which enlarge on the application of the obstructive theory of the origin of appendicitis. The general plan of this paper is to record investigations on the following points:

1. The degree and nature of the muscular activity of surviving excised human appendixes, as determined by means of water bath studies.

From the Department of Surgery, University Hospitals.

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A condensation of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. Wangensteen, O. H., and Dennis, C.: (*a*) Experimental Proof of the Obstructive Origin of Appendicitis in Man, Ann. Surg. **110**:629, 1939; (*b*) The Production of Acute Appendicitis (with Rupture) in Higher Apes by Luminal Obstruction, Surg., Gynec. & Obst. **70**:799, 1940.

2. Wangensteen, O. H., and Bowers, W. F.: An Experimental Study of the Obstructive Factor in the Genesis of Acute Appendicitis, Tr. West. S. A **45**:195, 1935.

2. The muscular activity of the human appendix as seen in specimens in situ made available by appendicostomy.

3. The importance of the neuromuscular mechanism of the appendix, evaluated through the action of drugs.

4. The absolute resistance to outflow (of fluid through the appendix into the cecum) and its relation to disease of the appendix.

5. The role of neuromuscular activity in initiating acute appendicitis.

6. The relation of muscular activity to appendical pain and the effect of epinephrine on it.

7. The contribution of the obstructive theory in the etiology of appendicitis to the explanation of the cause of peritonitis in certain cases (data on seepage through the appendical wall).

8. The relation of increased intraluminal tension to rupture.

9. The relation of the observations on neuromuscular activity to the gross and microscopic pathologic observations.

II. SURVEY OF THE LITERATURE ON THE NATURE OF THE MOVEMENTS OF THE HUMAN APPENDIX

A. *Motility of the Excised Ileum.*—Although Haffter [3] first discovered that excised intestine will continue to contract rhythmically, the bulk of the early work in this field was done by Magnus,[4] who showed that with proper recording devices both layers of muscle could be shown to perform small regular "pendular" contractions with a period of five to seven seconds and also peristaltic or tonus waves of greater amplitude and with a period of twenty to one hundred seconds. The presence of dextrose or the absence of oxygen bubbling through Locke's solution which he used as a medium proved inhibitory to continued activity. Gunn and Underhill [5] showed ten years later that these contractions are independent of any of the nerves of the intestine and therefore are myogenic in origin.

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3. Haffter: Neue Versuche ueber den Nervus splanchnicus, Ztschr. f. rat. Med. **4**:322, 1854; cited by Magnus.[4a]

4. Magnus, R.: (*a*) Versuche am überlebenden Dünndarm von Säugetieren: I. Mitteilung, Arch. f. d. ges. Physiol. **102**:123, 1904; (*b*) II. Mitteilung. Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung, ibid. **102**:349, 1904; (*c*) III. Mitteilung. Die Erregungsleitung, ibid. **103**:515, 1904. (*d*) IV. Mitteilung. Rhythmizität und refraktäre Periode, ibid. **103**:525, 1904. (*e*) V. Mitteilung. Wirkungsweise und Angriffspunkt einiger Gifte am Katzendarm, ibid. **108**:1, 1905.

5. Gunn, S. H., and Underhill, S. W. F.: Experiments on Surviving Mammalian Intestine, Quart. J. Physiol. **8**:275, 1914.

Alvarez and several co-workers[6] found that best rhythmic movements in the water bath could be obtained if the specimen were chilled in Locke's solution for a few hours before the study and also that if the muscle is to survive abundant oxygen must be supplied for the specimen or metabolism must be checked by refrigeration. He emphasized the myogenic nature of the rhythmic contractions seen in the intestine and championed the theory that gradients of various manifestations of physiologic activity, such as the rate of spontaneous rhythmic contractions, the rate of oxygen usage, the rate of carbon dioxide output and the lactic acid content of the resting muscle, determine the movements of the intact bowel. In any excised segment of small bowel, for instance, he found the cephalad portion to have the fastest rate of rhythmic contraction and therefore to determine the rate of contraction of the entire segment and the direction of propulsion of the contents, just as the area of fastest rhythmicity in the heart, the sinoatrial node, sets the pace for the whole organ.

B. *Motility Studies on the Surviving Excised Human Appendix.*—The surviving excised human appendix has been studied in similar fashion by a number of workers,[7] most of whom used Magnus' methods

6. (*a*) Alvarez, W. C.: Differences in the Action of Drugs on Different Parts of the Bowel, J. Pharmacol. & Exper. Therap. **12**:171, 1918; (*b*) Physiological Studies on the Motor Activities of the Stomach and Bowel in Man, Am. J Physiol. **88**:650, 1929; (*c*) The Mechanics of the Digestive Tract, ed. 2, New York, Paul B. Hoeber, 1919. (*d*) Alvarez, W. C., and Hosoi, K.: The Latent Period of Intestinal Muscle, Am. J. Physiol. **89**:201, 1929. (*e*) Alvarez, W. C., and Mahoney, L. J.: The Myogenic Nature of the Rhythmic Contractions of the Intestine, ibid. **49**:421, 1922. (*f*) Asciano, H., and Alvarez, W. C.: Factors That Influence the Conservation of Intestinal Rhythmicity After Death, Am. J. Physiol. **90**:611, 1929.

7. (*a*) Aschoff, L., and Pokorny, O.: Ueber die Beweglichkeit des Wurmfortsatzes, Deutsche Ztschr. f. Chir. **203**:175, 1927. (*b*) Cross, D. G. T. K.: The Action of Physostigmine (Eserine) and Pituitrin, Brit. M. J. **1**:9, 1924. (*c*) Gunn, J. A., and Whitelocke, R. H. A.: Observations on the Movements of the Isolated Human Vermiform Appendix, Brit. J. Surg. **2**:92, 1914. (*d*) Hara, S., and Uehara, T.: Pharmakologie über den ausgeschnittenen Wurmfortsatz des Menschen, Jap. J. M. Sc., IV, Pharmacol. **10**:130, 1937. (*e*) Holm, K.: Untersuchungen am ueberlebenden menschlichen Wurmfortsatz, Arch. f. d. ges. Physiol. **197**:411, 1922. (*f*) Miller, J., and Mann, J.: The Muscular Movements of the Appendix and Their Relation to Appendicitis, Tr. Roy. Soc. Canada (Sect. V) **22**:311, 1928. (*g*) Ricker, G.: Pathologie als Naturwissenschaft, Berlin, Julius Springer, 1924; cited by McCloskey.[27e] (*h*) Rössle, R.: Die Beweglichkeit des Wurmfortsatzes, Beitr. z. path. Anat. u. z. allg. Path. **77**:121, 1927. (*i*) Ruf, S.: Die Appendicitis im Lichte der Ricker'schen Gefässnerventheorie, ibid. **75**:135, 1926. (*j*) Ulrich, L.: Ueber die motorischen Funktionen der Appendix, Deutsche Ztschr. f. Chir. **212**: 119, 1928.

and recorded contractions of the longitudinal muscle by means of a muscle lever. Ruf [7f] and Aschoff and Pokorny [7a] maintained that the movements of the appendix are too feeble to prevent the stasis which Aschoff [8] considered essential to the development of appendicitis. Ricker [7g] thought that there were movements fully as active as those of the ileum, but most workers have been inclined to favor a middle stand. Ulrich,[7j] the only one who has studied the activity of the circular muscle, attached a writing lever by a thread to the serosa opposite an anchored point; by the use of several of these, he tried unsuccessfully to demonstrate peristaltic activity in his specimens.

C. *Motility Studies on the Human Appendix Through the Medium of Roentgenology.*—A considerable number of roentgenologists have tried to elucidate the problem of appendical movements by means of the visualization which is frequently obtainable in the course of gastrointestinal roentgen ray studies.[9] It is the consensus that active movement takes place and that filling and emptying occur in the presence of a filled cecum. Westphal and Schmidtlein administered large (10 mg.) doses of pilocarpine intravenously during observation, and they reported spasm of the proximal portion, or "antrum," of the appendix. Wildegans, using roentgenocinematography, described definite peristaltic movements commencing at the tip and moving proximally.

D. *Pharmacologic Studies of the Neuromuscular Mechanism of the Human Appendix.*—1. Barium Chloride: Magnus [4e] observed the stimulating action of barium chloride in small concentrations (1:10,000) on both the rhythmic contractions and the tonus of excised pieces of cat intestine. Various workers have confirmed this finding both for the ileum and for the human appendix in the water bath.[10] Alvarez has shown that electrical variations occur in the muscle when contractions have not yet appeared and likened the barium in effect to a "clutch" connecting the muscle to an idling motor.[6e]

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8. Aschoff, L.: Appendicitis: Its Etiology and Pathogenesis, London, Constable & Co., 1931.

9. (*a*) Cohn, M.: Die Appendix im Röntgenbilde, Berl. klin. Wchnschr. **50**:326, 1913. (*b*) Hubeny, M. J.: The Appendix with Especial Reference to Peristalsis, Am. J. Roentgenol. **5**:293, 1918. (*c*) Schmidtlein, E.: Ueber die aktive Beweglichkeit und den Entleerungsmechanismus des Wurmfortsatzes, Fortschr. a. d. Geb. d. Röntgenstrahlen **44**:141, 1931. (*d*) Westphal, K.: Bewegungsmechanismus, Resorption und Pathologie des Wurmfortsatzes, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**:99, 1930. (*e*) Wildegans, H.: Medizinische Kinemato- und Photographie: VII. Die Bewegungen des Dickdarms einschliesslich des Wurmfortsatzes im röntgenkinematographischen Bilde, Deutsche med. Wchnschr. **58**:1569, 1932.

10. Alvarez.[6e] Gunn and Underhill.[5] Hara and Uehara.[7d] Holm.[7e]

2. Epinephrine: Magnus [4e] showed a diminution in tone and a temporary abolition of movements in cat intestine by the addition of epinephrine hydrochloride to a concentration of 1 : 20,000,000, and Gunn and Whitelocke [7c] showed a similar effect with higher concentrations (1 : 250,000) in the human appendix. Hara and Uehara [7d] observed a stimulating action of epinephrine if added in sufficiently low concentration.

3. Ephedrine: No mention has been found in the literature on the action of ephedrine on the appendical musculature.

4. Amphetamine: Myerson and Ritvo [11] and Beyer [12] agreed that amphetamine (benzedrine) sulfate administered orally causes relaxation of spasm throughout the alimentary tract, but Beyer described a brief preliminary increase in tone and rate of rhythmic contraction occurring before the inhibitory effect.

5. Acetylcholine: Starling [13] stated that acetylcholine causes contraction of the intestinal musculature, but Puestow,[14] on the basis of observations on a patient with cecostomy and eversion of the posterior cecal wall with inclusion of loops of small intestine, reported that acetylcholine caused increased activity in the small bowel and decreased activity in the colon. No reports have been found relating to its effect on the appendix.

6. Physostigmine: In his patient Puestow [14] found the reaction to physostigmine to be similar to that to acetylcholine. Hara and Uehara [7d] reported increased tonus and activity in the surviving human appendix.

7. Pilocarpine: Magnus [4e] was much impressed by the rise in tone and increase in rate of rhythmic contractions of the intestine caused by the addition of 2 to 30 mg. of pilocarpine to a bath of 200 cc. of Ringer's solution. The effect has been corroborated for the bowel [5] and for the appendix in the water bath.[15] Marked contraction of the appendix in response to the drug has been observed directly by laparoscopy [16] and also on roentgenologic examination (Schmidtlein [9c] and Westphal [9d]).

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11. Myerson, A., and Ritvo, M.: Benzedrine Sulfate and Its Value in Spasm of the Gastro-Intestinal Tract, J. A. M. A. **107**:24 (July 4) 1936.

12. Beyer, K. H.: Gastric Emptying as Influenced by Benzedrine Sulfate, Am. J. Physiol. **123**:16, 1938.

13. Starling, E. H.: Principles of Human Physiology, ed. 7, Philadelphia, Lea & Febiger, 1936.

14. Puestow, C. B.: The Action of Drugs on Intestinal Motility, Am. J. Physiol. **123**:165, 1938.

15. Gunn and Whitelocke.[7c] Hara and Uehara.[7d] Miller and Mann.[7f]

16. Kalk, H.: Eine Beobachtung über die Bewegungsvorgänge an der Appendix, Deutsche med. Wchnschr. **63**:772, 1937.

8. Atropine: There is unanimity of opinion among investigators that atropine abolishes the stimulating action of physostigmine, pilocarpine and acetylcholine [17] in the appendix, as well as in other parts of the bowel. Magnus [4e] found also that small doses of atropine sulfate (1:2,000) without previous medication caused stimulation of pieces of cat ileum and made the rhythmic contractions more regular. Solutions as concentrated as 1:1,000 made rhythmic movements at first more regular and then weaker, with complete cessation when the concentration was increased to 1:300. Holm [7e] and Hara and Uehara [7d] failed to find the stimulating action on surviving human appendixes.

9. Nicotine: Magnus [4e] observed that a 1:4,000 concentration of nicotine stopped rhythmic movements of the intestine for a few minutes, after which the movements were resumed in the continued presence of the drug; a gradual increase in tonus also occurred over a period of half an hour. No reports have been found on the effect on the appendix.

10. Morphine: In his patient, previously described, Puestow [14] observed increased activity in the small bowel and decreased activity in the colon after morphine had been given. Dvorak and his associates [18] found morphine to increase the intestinal tone and peristaltic activity of the obstructed small intestine of the dog. Krueger [19] summarized the literature on the effect of morphine on the intestinal tract and mentioned increased tone and increased peristaltic activity, though with decreased amplitude and no change in pendular movements in the large bowel; in the small intestine, on the other hand, morphine was reported to cause an increase in tone, in amplitude and in frequency of movements but a diminution in propulsive activity. Hara and Uehara [7d] stated that the effect on the appendix varied with the dose but that increased activity could be obtained.

11. Papaverine: Hara and Uehara [7d] observed obliteration of the barium effect and diminution of tone by addition of papaverine to the bath.

PART 2. EXPERIMENTAL PROCEDURES AND OBSERVATIONS

III. MATERIALS USED IN THIS STUDY

Observations were made on 272 excised appendixes. Two hundred and twenty-seven of these came from the operating rooms of the

17. Magnus.[4e] Gunn and Underhill.[5] Gunn and Whitelocke.[7c] Hara and Uehara.[7d] Holm.[7e] Cohn.[9a] Schmidtlein.[9c] Westphal.[9d] Kalk.[16]

18. Dvorak, H. S.; Carlson, H. A.; Erickson, T. C.; Smith, V. D., and Wangensteen, O. H.: Influence of Morphine on Intestinal Activity in Experimental Obstruction, Proc. Soc. Exper. Biol. & Med. **28**:434, 1931.

19. Krueger, H.: The Action of Morphine on the Digestive Tract, Physiol. Rev. **17**:618, 1937.

University Hospitals, 16 from the Minneapolis General Hospital [20] and 18 from the morgue of the University Hospitals. In 66 instances observations were made in the operating room. Eleven additional appendixes were studied in situ by means of appendicostomy with delayed opening. Three ureters also became available for study, 1 after excision and 2 while still in the patient.

At the University Hospitals appendicitis is treated by conservative measures if the history, signs and symptoms suggest that frank rupture has occurred.[21] These measures include duodenal siphonage through an inlying nasal catheter, abdominal hot packs and oral administration of fluids. Six to eight weeks later the appendix is removed. An appendix obtained at such an appendectomy after an interval is called an "interval specimen." It was thus possible to study many appendixes for late effects of acute inflammation, as well as normal and acutely inflamed specimens.

IV. WATER BATH STUDIES TO INVESTIGATE THE DEGREE AND NATURE OF MUSCULAR ACTIVITY OF SURVIVING HUMAN APPENDIXES

A. *Apparatus.*—As emphasis has been placed on the resistance to flow of fluid through the lumen of the appendix by correlation with the clinical diagnosis [22] and by production of appendicitis by ligature obstruction,[1] variations in resistance to flow have been recorded rather than the contractions of the circular muscle.

As illustrated diagrammatically in figure 1, the bath used in experiments for this purpose consisted of a horizontal tray containing 180 cc. of fluid, kept at 37 C. by a thermostat. At one end of the tray a glass cannula was fixed in position below the level of the fluid in the bath. A tube connected this cannula to an elevated flask of Locke's solution without dextrose fitted with an adjusting valve and a gravity drip bulb and to a recording mercury manometer. A pulley was mounted at the far end of the bath in order that a thread attached to the end of the specimen opposite the cannula might be led to a recording lever. An oxygen jet was fixed in one corner of the bath, and the fluid coming to the cannula was preheated to the temperature of the bath in a submerged coil of tubing, not shown in the diagram.

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20. The surgical staffs of the University Hospitals and of the Minneapolis General Hospital assisted in the execution of this study.

21. (*a*) Adams, J. M., and Bancroft, P. M.: The Conservative Management of Appendiceal Peritonitis in Children, J. Pediat. **12**:298, 1938. (*b*) Ochsner, A.: Conservative Treatment of Appendical Peritonitis, New Orleans M. & S. J. **87**:32, 1934.

22. Wangensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W. P.: Studies in the Etiology of Acute Appendicitis: The Significance of the Structure and Function of the Vermiform Appendix in the Genesis of Appendicitis; a Preliminary Report, Ann. Surg. **106**:910, 1937.

By virtue of the arrangement of the apparatus, the record obtained indicated the resistance to flow of fluid through the lumen and the variations in length of the specimen.

B. *Procedure.*—The freshly excised appendix was wrapped in gauze soaked in saline solution and placed in an ice box at a temperature of 2 to 7 C. After a few hours or days the specimen was transferred to the bath, which had been filled with Locke's solution without dextrose at the same low temperature. The tip of the appendix was amputated, and the distal end of the remaining specimen was slipped over the

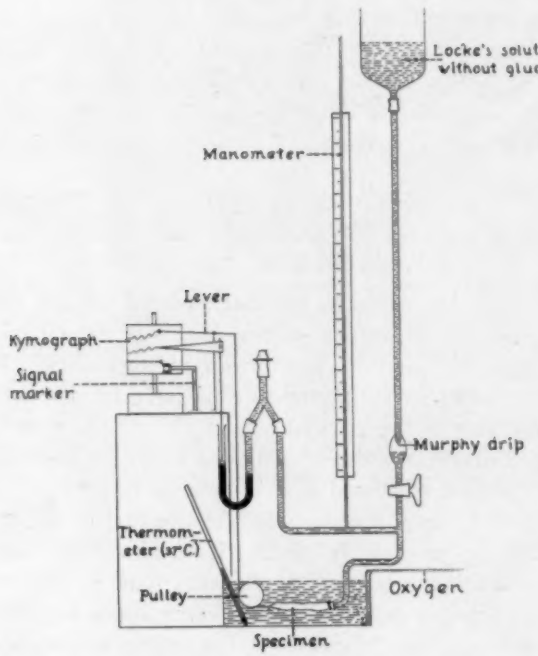

Fig. 1.—Schematic drawing of the apparatus used for water bath studies of surviving excised human appendixes.

cannula of the bath and securely tied. A thread was passed through one wall of the proximal end of the appendix, passed around the pulley and led vertically up to the writing lever. A kymograph fitted with smoked paper for recording was approximated to the writing points of the lever and the mercury manometer. The flow of oxygen was started at once, and the temperature was gradually raised, reaching 37 C. in from thirty to forty minutes as a rule. The rate of flow through the lumen was usually 20 to 60 drops per minute, excess fluid leaving the bath by an overflow drain.

In all kymographic tracings shown, pressures are recorded in centimeters of water, and each rise of 20 cm. above the standard line indicates a 2 mm. shortening of the specimen.

C. *Observations.*—Most appendixes presented active rhythmic contractions both of the longitudinal muscle and of the circular muscle, those of the latter reflected by variations in pressure. As the temperature was raised, marked diminution and then a gain in tonus occurred, the latter appearing near body temperature and usually in association with the appearance of slow, large rhythmic contractions of both layers

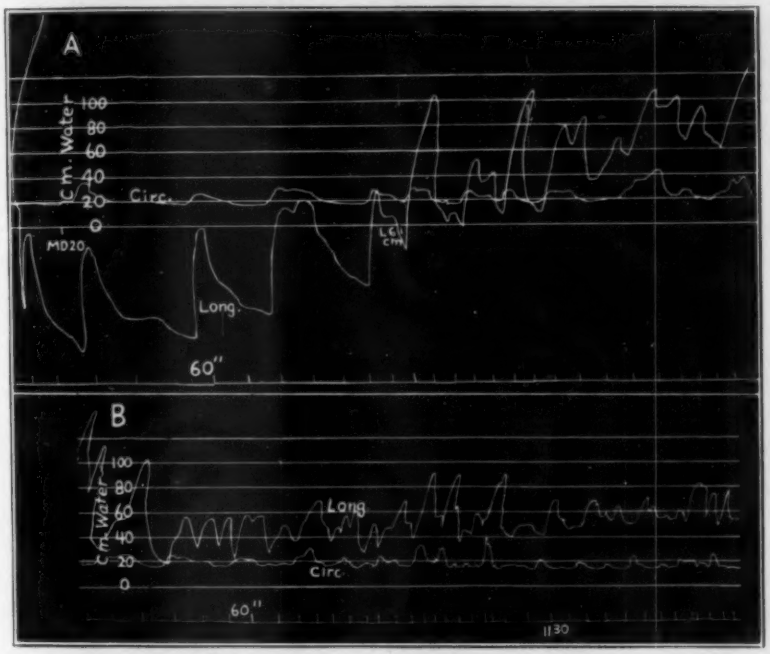

Fig. 2.—Kymographic records of the contractions of a surviving excised human appendix. *A*, early contractions; *circ.* indicates resistance to flow of fluid through the lumen (activity of the circular muscle), and *long.* indicates activity of the longitudinal muscle. The waves are large and slow, and an increase in tone is shown in the longitudinal layer. *B*, contractions during the second hour in the water bath. Changes in tonus are no longer marked, and the waves are more regular.

of muscle (fig. 2 *A*). After thirty to sixty minutes of movements, the changes in tonus became minimal and the waves faster and more regular, with an interval of ten to forty seconds (fig. 2 *B*). The fine pendular waves with a period of three to ten seconds described by Gunn and Whitelocke [7e] were only occasionally seen in the water bath (though they were usually present in appendicostomy tracings). The rhythmic

contractions in the two muscle layers were usually but not necessarily synchronous, either layer occasionally presenting waves with no change in the other. An hour or two after the start of distinct waves a final loss of tone began gradually to occur, and the waves became smaller in amplitude, more irregular and usually faster, finally ceasing altogether.

D. *Influence of Inflammation on the Motility of Excised Appendixes.*—Of all the previous investigators, only Ulrich [7j] and Hara and Uehara [7d] observed poorer contractions in inflamed specimens, and some made a point of stressing the lack of influence of inflammation (Gunn and Whitelocke [7e] and Rössle [7h]). The behavior of specimens showing varying degrees of involvement is indicated in table 1, which shows that the degree of inflammation plays a decisive role in preventing subsequent development of activity. That the interference with movement is not a variation from person to person, with incidental inflammation, is

TABLE 1.—*The Effect of Acute Inflammation on the Occurrence of Spontaneous Rhythmic Contractions of Excised Human Appendixes in the Study Bath*

	Number of Specimens			Per Cent of Specimens Showing Rhythmic Activity
	Strong Rhythmic Contractions	Weak Rhythmic Contractions	No Activity	
Appendixes showing no microscopic evidence of inflammation	21	8	3	91
Acutely inflamed appendixes	31	16	16	75
Gangrenous appendixes	0	2	7	22
Total	52	26	26	75

indicated by two specimens a half of each of which was gangrenous and failed to show rhythmic movements, the other half showing less marked change and presenting active contractions.

E. *Influence of Chilling the Specimen on the Appearance of Motility.*—Gunn and Underhill [5] and Asciano and Alvarez [6f] found that they were more successful in water bath experiments if the specimen was cooled before use. An attempt was made to assay the importance of this factor in the present study. Seven specimens were transferred directly from patient to study bath. In contrast to the observations in table 1, no waves appeared in 4 specimens, very poor ones in 2 and good ones in only 1.

Faradic stimulation was utilized on several specimens and regularly caused elevation in resistance to outflow, with a latent period of one to four seconds, but in a chilled specimen no effect was observed on the maximal stimulus obtainable with two dry cells and a Harvard inductorium, so much had the irritability of the appendix been depressed. It was concluded, therefore, that chilling the specimen permits manipulation of the appendix and adjustment of the apparatus without stimulation of the appendical musculature.

V. CONFIRMATION OF NEUROMUSCULAR ACTIVITY OF THE HUMAN APPENDIX BY STUDY OF SPECIMENS IN SITU MADE AVAILABLE BY APPENDICOSTOMY

A. *Procedure.*—Ten patients presenting cancer of the large bowel and 1 presenting ulcerative colitis were subjected to laparotomy for diversion of the fecal stream; at the time of this operation the appendix was incidentally delivered through a stab wound in the right lower abdominal quadrant sufficiently large to preclude compression of appendix or mesentery. After five or six days the tip was amputated and a no. 8 French soft catheter with the end cut off squarely was tied into the lumen.[22] The resistance to the passage of fluid through the appendix into the cecum was determined continuously by an arrangement of flask, tubing and manometers similar to that previously described for the water bath experiments. The rate of flow was usually adjusted at 15 to 20 drops per minute.

B. *Observations.*—1. In the Fasting State: In fasting patients three types of waves were discernible. Pendular contractions with a period of seven to ten seconds and an amplitude of 2 to 5 cm. of water pressure were superimposed on what will be termed "small tonus waves," coming every thirty to ninety seconds and having an amplitude of as much as 20 cm. of water at times (fig. 3*A*). For the third type there were what will be termed "large tonus waves," or periods of increased activity, coming every ten to twenty minutes. Between these active periods only the pendular and smaller tonus waves were in evidence, and the resistance to flow at these times, the "basal level," usually hovered somewhere between 15 and 30 cm. of water. As an active period approached, the mean level rose gradually to a pressure 20 to 30 cm. above the basal level, and the size of the individual small tonus waves also increased.

The tracings under these circumstances, therefore, differed from the tracings of resistance to flow in the water bath chiefly in the higher basal level (usually 15 to 30 cm., as against 8 to 10 cm. in the bath) and in the presence of large tonus waves. It is because of the presence of the latter waves that the term neuromuscular rather than muscular is used, for these waves imply more than the rhythmic myogenic contractions seen in the water bath. An increase in the rate of flow of fluid was found to elevate the observed resistance to flow very little. In 1 case the basal level was between 20 and 25 cm. of pressure at 30 drops per minute but well above 30 cm. at 100 drops.

2. Comparison of Appendical Resistance to Outflow with the Intracecal Pressure: As has been previously reported,[22] the resistance to flow in an appendix in situ made available by appendicostomy is not

due to the intracecal pressure, for if the catheter is slipped through the appendix and into the cecum, the resistance drops to 2 to 3 cm. of water pressure.

In the patient with ulcerative colitis, a terminal ileostomy was made in addition to an appendicostomy, and it was possible to insert a catheter into the lower segment of ileum, through the ileocecal sphincter and into the cecum, permitting simultaneous recordings of intra-appendical and intracecal pressures. In the vast bulk of the records made over a period of four days the two curves were roughly parallel, with the cecal

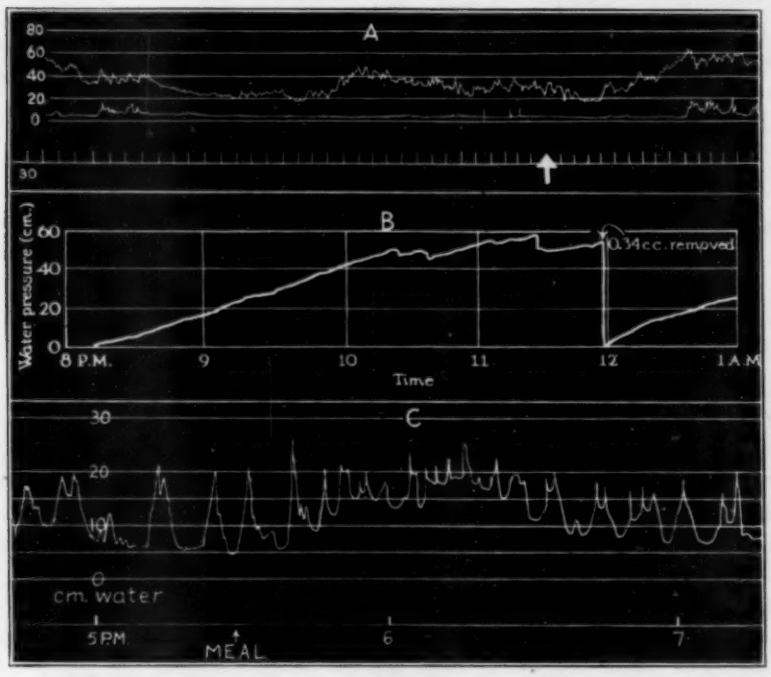

Fig. 3.—*A*, kymograph record of variations in resistance to outflow of an appendix made available by appendicostomy (upper curve). Pendular waves, small tonus waves and large tonus waves may be seen. The relative level of cecal pressure and activity (obtained by insertion of a catheter through a terminal ileostomy opening, through the ileocecal valve and into the cecum) are indicated in the lower curve. The stimulating effect of subcutaneous injection of 12 mg. of morphine sulfate (arrow) is also shown; this effect was not obtained in the other two trials. *B*, pressure tracing made with a catheter in a specimen made available by appendicostomy (Wangensteen, Buirge, Dennis and Ritchie [22]). A spontaneous rise in pressure from atmospheric to more than 50 cm. of water in three hours is shown. The lumen of the appendix was patent. The sudden falls and repeated rises at the top of the curve are considered due to a balance between continued secretion and rhythmic variations in resistance to outflow. *C*, tracing of a kymographic record showing the effect of the ingestion of food on the resistance to outflow in an appendicostomy specimen.

tracing about 20 cm. below the appendical; but on a few occasions the intracecal pressure was observed to rise above the level of the appendical resistance, particularly if the flow of fluid was stopped, an observation which may help to clarify the roentgenologic observation of filling of the appendix.

3. Proof That the Absolute Resistance to Outflow Is the Pressure Actually Present in the Appendix: It has been shown [18] that the normal mucosa of the human appendix secretes fluid at the rate of from 2 to 3 cc. per day. This constant flow of fluid, slow though it is, coupled with the previously demonstrated resistance to outflow would suggest that the very small amount of fluid normally present in the lumen of the appendix is under tension.

In order to test whether this actually is the case, a small volume manometer (requiring 0.62 cc. to raise the reading from 0 to 100 cm. of water) was connected by a closed system to the tip of an unobstructed appendix made available by appendicostomy. The fluid secreted by the organ elevated the pressure consistently, on one occasion to over 50 cm. of water in less than three hours (fig. 3 *B*). At about 50 cm. of pressure a sudden drop of 3 to 4 cm. occurred, only to be followed by a rise and then another drop, etc. This type of curve is interpreted as due to a balance between fluid secretion and the resistance to outflow varied by rhythmic contractions in the circular muscle. It follows that the intraluminal tension normally must be the level of the resistance to outflow.

4. Effect of the Ingestion of Food on the Resistance to Outflow in the Appendix in Situ Made Available by Appendicostomy: The type of fasting curve just described was altered to a considerable extent by the ingestion of food. The basal level rose 10 to 15 cm. as if the periods of increased activity had become merged, and this greater activity persisted for about two hours before again settling to the fasting level (fig. 3 *C*). In 1 instance simultaneous cecal readings were possible; the intracecal pressure rose only 6 to 8 cm. but might have risen higher had the flow of chyme from the ileum not been interrupted by ileostomy.

VI. EVALUATION THROUGH DRUG ACTION OF THE IMPORTANCE OF THE NEUROMUSCULAR MECHANISM OF THE APPENDIX

A. *Procedures.*—1. Water Bath Experiments: In attempting to evaluate the action of drugs on appendixes in the water bath, rhythmic contractions were allowed to develop until they had become fairly uniform. The agent was then added to the solution at a corner of the chamber as far from the specimen as possible. Unless otherwise indicated, the drug was added in aqueous solution and only one drug was used on each specimen.

Many of the specimens used were found on subsequent microscopic examination to be acutely inflamed. With each drug (with the exception of acetylcholine) experiments were performed until comparison of the effects in inflamed and in uninflamed appendixes could be made. No alteration of drug effect by any degree of inflammation was found, provided only that spontaneous movements appear before administration of the drug.

2. Appendicostomy Experiments: In assaying the effects of drugs on appendixes in situ made available by appendicostomy, the subcutaneous route of administration was usually followed. The drug was not given until three hours after the last meal, and administration was regularly preceded by a one hour control recording.

B. *Effect of Drugs on the Neuromuscular Activity of the Appendix.*—1. Barium Chloride: In many instances in which appendixes were being studied in the bath it was found that the addition of 30 to 50 mg. of barium chloride crystals hastened the initiation of contractions, and in some cases it seemed probable that deterioration would have occured without manifestation of contractions at all had the drug not been added. It was used in about half the experiments (fig. 4 *A*). The effect of previous addition of this quantity of barium chloride to the bath on the responses to the drugs used was carefully checked for all the drugs tested except acetylcholine, and only in the case of amphetamine was any difference encountered.

2. Epinephrine: In 1 instance a concentration of 1:900,000 of epinephrine caused a very slight increase in amplitude of tonus waves in the water bath; this, however, was the only change suggesting stimulation, for the rate of contraction was slowed slightly and the pendular contractions, which had been evident before the medication, disappeared afterward (fig. 4 *B*). In 8 other cases larger concentrations (up to 1:90,000) caused a loss of tone in both layers of muscle, reducing the size of the waves in 1 instance and abolishing them altogether in the remainder (fig. 4 *C*).

Epinephrine hydrochloride (1:1,000 solution) was given subcutaneously in 0.67 cc. doses to each of 3 patients with appendicostomies. In all cases a distinct quieting effect was apparent. In 1 case all the great and small tonus waves were eliminated for nearly an hour and the mean level of pressure was lowered 5 cm. of water; in the others, although the general pressure rose somewhat when the next period of activity was to be expected, the rise was less marked than in active periods before the medication, and the smaller tonus and pendular waves were nearly lost (fig. 4 *D*).

3. Ephedrine: In the water bath ephedrine sulfate was tested in thirteen experiments on 10 specimens in concentrations varying from 1:3,600 to 1:1,500, and the effect varied widely under similar circum-

stances, regardless of the degree of inflammation and regardless of the presence or absence of barium chloride. The commonest effect was a decrease in amplitude with an increase in rate of rhythmic contractions in both layers of muscle without definite change in tonus. In 4 instances the drug caused complete loss of rhythmic contractions.

The subcutaneous injection of 45 mg. of ephedrine sulfate in 2 cases in which appendicostomy had been performed eliminated the small tonus waves and weakened the pendular waves, abolishing them in 1 case. The effect lasted about forty minutes.

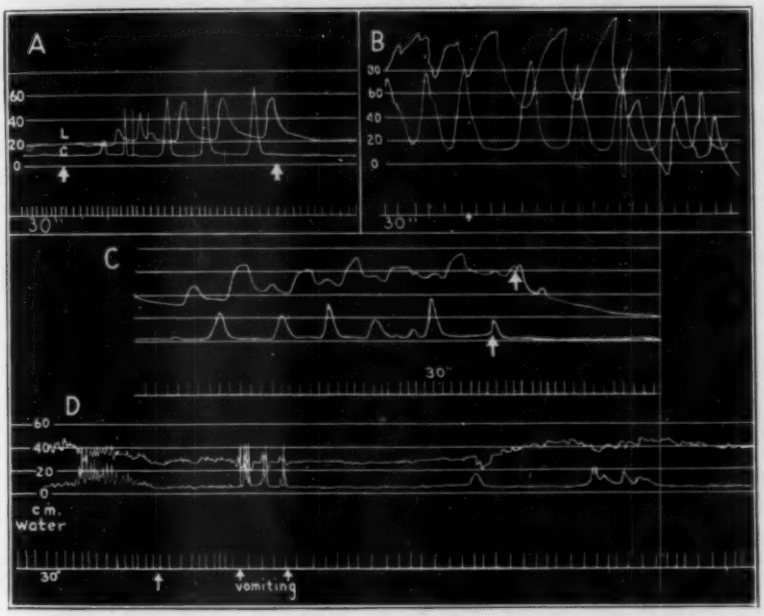

Fig. 4.—Kymographic records showing: (*A*) the efficacy of barium chloride, 1:4,000 (arrow at the left), in initiating rhythmic contractions in an excised appendix in the water bath and the abolition of the effect of the barium by papaverine, 1:11,000 (arrow at the right). *B*, slight increase in the amplitude of contraction obtained in the water bath on the addition of epinephrine to a concentration of 1:900,000 (arrow). The rate of contraction was slowed somewhat, and the pendular waves were abolished. Near the end of the record a correction was made to keep the pointer from rising over the top of the drum. This is the only instance in which any semblance of stimulation was obtained from epinephrine. *C*, the usual response of the surviving excised appendix to epinephrine hydrochloride, 1:180,000 (arrow). *D*, the effect of the subcutaneous injection of 0.67 cc. of epinephrine hydrochloride 1:1,000 on the resistance to flow of fluid at 20 drops per minute through the lumen of an appendicostomy specimen into the cecum (above) and on the intracecal pressure (below). The marked excursions of the cecal pressure shortly after the medication were due to vomiting. Loss of pendular waves in both the cecum and the appendix occurred, and the appendical resistance rose less high during the large tonus wave after the administration of epinephrine than before.

4. Amphetamine: Amphetamine sulfate [23] was tested in seventeen water bath experiments on 10 specimens, including a piece of rabbit ileum. In eight experiments barium chloride was omitted, and concentrations of amphetamine sulfate from 1:1,000 to 1:2,000 caused an increase both in tonus and in amplitude of contraction waves in both layers of muscle (fig. 5 *A*), while more dilute concentrations (1:4,000) caused no noticeable change. The segment of rabbit ileum, on the other hand, lost considerable tone when exposed to 1:4,000 amphetamine sulfate and the rhythmic contractions were first inhibited and then abolished by comparable additions of the drug (fig. 5 *B*). In the presence of barium chloride the more dilute solution of amphetamine sulfate (1:4,000) caused varied results, but in concentrations above 1:2,000 rhythmic contractions were abolished with no change in tone.

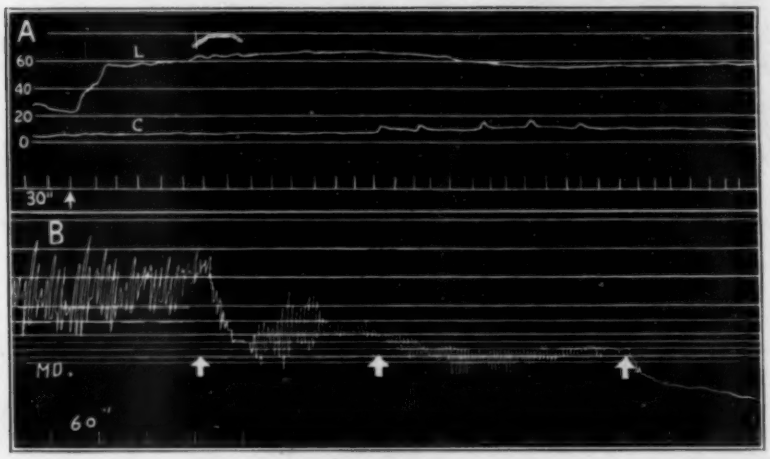

Fig. 5.—*A*, the stimulating effect on the excised human appendix of 1:1,000 amphetamine sulfate (arrow) in the absence of barium. There is a rise in tone in both layers, with a loss of rhythmic contractions in the outer layer, and an increase in contractions in the circular muscle. *B*, reduction in tone of a piece of rabbit ileum by the addition of amphetamine sulfate (1:4,000) to the water bath (200 cc.). Decrease in rhythmic contractions also occurred on further addition of the drug (second arrow, 50 mg.; third arrow, 100 mg.).

In the appendicostomy studies, 30 mg. of amphetamine sulfate was given by mouth in 3 instances, in 2 of which no effect could be seen. In the third instance this dose was administered ten minutes after 12 mg. of morphine sulfate had been injected subcutaneously. Some hyperactivity from the morphine had already appeared, but in another fifteen minutes greater activity became apparent in both the cecum and

23. The amphetamine sulfate was supplied by Smith, Kline & French Laboratories, Philadelphia.

the appendix than was evident on any other occasion in which morphine was given; the basal level dropped to below 20 cm. of water for six minute periods, alternating with periods of equal length during which violent rapid waves were present, the change lasting over an hour.

The findings with regard to this drug differ considerably from any found in the literature thus far, although Beyer [12] found that it caused a preliminary increase in tonus and rate of rhythmic contraction, followed in a few minutes by inhibition of contractions and return of tonus to normal. The startling difference between the response of the human appendix and that of the ileum of the rabbit, together with the prolonged hyperactivity of the appendicostomy specimen when morphine in conjunction with amphetamine had been administered, strongly suggest that there is here a difference between the response of the appendix and that of the remainder of the intestinal tract.

5. Acetylcholine: Acetylcholine hydrobromide in a concentration of 1:1,000,000 in the bath caused a moderate rise in resistance to flow and marked shortening of the specimen, with temporary disappearance of most of the big waves in both layers.

Ten milligrams given subcutaneously to a patient with an appendicostomy resulted in a great enlargement in the pendular and small tonus waves for over thirty minutes, with an elevation of the basal pressure of some 10 cm. for several minutes.

6. Physostigmine: This drug (physostigmine sulfate) was used only in the water bath, where in 10 specimens all concentrations from 1:20,000 to 1:4,000 caused increased tone in both layers of muscle, although the effect of the smaller doses was transitory. Smaller concentrations served as a stimulus to rhythmic contractions, in some cases even starting them when the specimen had been quiet previously, but higher concentrations seemed to interfere with motility.

7. Pilocarpine: Pilocarpine hydrochloride also was used only in the bath. In 4 specimens a concentration of 1:200,000 caused an increase in tone in both layers of muscle with a decrease in the size of the waves, and in 1 case a concentration of 1:50,000 caused shortening and loss of rhythmic contractions in both layers. These results are not in harmony with those of Gunn and Whitelocke,[7c] who found a concentration of 1:200,000 to stimulate spontaneous movement. The effect in the experiments reported here is very similar to that of the higher concentrations of physostigmine previously mentioned; it is as if rhythmic activity is inhibited because the stimulating action of the drugs prevents the muscle from relaxing between waves.

8. Atrophine: Atropine sulfate was studied in 6 water bath specimens. A concentration of 1:14,000 in 1 instance caused a slight increase in tonus and rate of rhythmic contractions in the longitudinal muscle

but no other suggestion of a stimulating action. Concentrations of 1:10,000 were adequate to nullify the effect of previously administered physostigmine or acetylcholine. A concentration of 1:7,000 caused a temporary loss of tone and activity in both layers. In a specimen in which activity had been stopped with increased tone by physostigmine (1:5,000) the addition of 1:1,000 atropine caused marked loss of tone and return of rhythmic contractions.

No effect on the resistance to outflow in the appendix was observed after the administration of 0.4 mg. of atropine sulfate to a patient with an appendicostomy.

The finding of a stimulating action caused by dilute solutions of atropine is in accord with the findings of Magnus on segments of cat ileum,[4e] results which Holm [7e] and Hara and Uehara [7d] failed to confirm in studies of the surviving appendix. It must be noted, however, that the dose which proved to have some stimulating action in the appendix was one seventh of that which Magnus found effective. The statement that the abolition of rhythmic contractions by higher concentrations of physostigmine and pilocarpine might be due to failure to allow relaxation between waves is of interest in connection with the restitution of rhythmic activity and the relaxation of the muscle brought about by the addition of atropine after higher concentrations of physostigmine had been exhibited.

9. Nicotine: Pure nicotine could not be obtained, but a crude preparation was used ("black leaf 40"), in concentrations from 1:12,000 to 1:120,000 in three water bath experiments. Addition of the drug to the water bath was followed by an immediate rise in tone in both layers and a simultaneous loss of rhythmic contractions. In two to three minutes the tone returned to normal and the rhythmic contractions recommenced in spite of the continued presence of the drug. These results are in essential agreement with the findings of Magnus,[4e] except that he observed no change in tonus immediately but only a gradual shortening in half an hour or more.

10. Morphine: In very dilute solutions morphine sulfate was without effect in three water bath experiments, but when a concentration of 1:7,000 was used (once with and once without barium) an initial slight relaxation of the longitudinal muscle was followed by marked shortening of both layers lasting less than a minute; the tone fell to less than the initial level within ten minutes, and nearly all waves were abolished at once (fig. 6).

Twelve milligram doses of morphine sulfate were administered on three occasions to patients with appendicostomies. Twice there was a quieting effect on the appendical activity, the higher waves being diminished in one instance and the peaks of activity being eliminated

altogether in the other. In the latter instance cecal activity increased until the general cecal pressure was at least as high as that of the appendix, a situation nowhere else encountered in these experiments. On a third occasion there was a rise in appendical resistance with parallel increase in cecal activity of marked degree (fig. 3 *A*).

The variability in the reaction to morphine in different subjects is less striking than the fact that two of the trials were on the same person, one causing definite stimulation and the other inhibition of movements.

11. Papaverine: In concentrations from 1:9,000 to 1:12,000 papaverine hydrochloride was effective in the water bath in stopping rhythmic contractions of the appendix without appreciable change in tonus regardless of whether barium had been added (fig. 4 *A*).

A 30 mg. dose of the drug administered intravenously was without effect on the resistance to flow in an appendicostomy preparation.

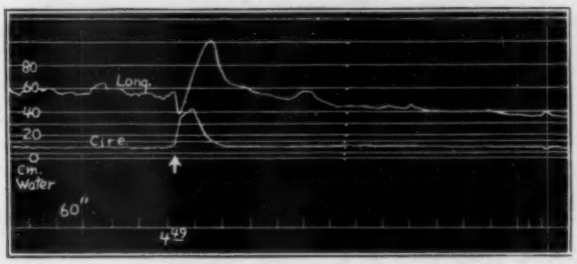

Fig. 6.—Kymographic record showing transitory contraction followed by loss of tone and most of movements of both layers of muscle of a surviving appendix induced by the addition (arrow) of morphine sulfate to a concentration of 1:7,000.

12. Prostigmine: Subcutaneous injection of 0.5 mg. of prostigmine methylsulfate caused a prolonged period of increased resistance to flow in an appendicostomy preparation, with increased size of the pendular and small tonus waves. Thirteen minutes later increased cecal activity also became evident. The effect was still plainly visible over an hour later.

Prostigmine was not used in the water bath.

13. Amyl Nitrite: The inhalation of amyl nitrite was without evident effect on two occasions, although the systemic reaction was pronounced.

14. Spinal Anesthesia: Seventy-five milligrams of procaine hydrochloride dissolved in 3 cc. of spinal fluid was given intrathecally to 1 patient. With the onset of anesthesia the basal level became elevated about 8 cm., returning to the original level of 35 cm. as sensation com-

menced to return thirty-five minutes later. Coupled with this change was a decrease in the eminence of the large tonus waves, which unfortunately had not been well marked initially.

15. Cocaine and Procaine: Masson [24] had described a "plexus of the intestinal mucosa" related to the argentaffin cells of the mucous membrane of the intestine and appendix. He enlarged on the "musculoneural" mechanism of the submucosal portion of the appendix.

In order to determine if either of these structures plays a role in the maintenance of a resistance to flow of fluid through the lumen of the organ, attempts were made to anesthetize, if possible, the nerves involved. With a moist chamber at 37 C. instead of a bath, cocaine hydrochloride solution was applied topically to 4 specimens and run into the lumen of another. A 0.5 per cent solution applied to the serosa increased the resistance to flow, while higher concentrations reduced it and caused relaxation of the longitudinal muscle, results in harmony with those described by Cushny,[25] which, he stated, were due to direct action on the muscle. Five cubic centimeters of a 2 per cent solution run through the lumen in five minutes caused no change of tone in either layer.

Instillation of 5 cc. of a 1 per cent solution of cocaine hydrochloride in an appendicostomy preparation over a five minute period was followed by no definite effect except that on several subsequent peaks of activity the pressure rose 30 to 40 cm. of water higher than the peaks before the administration of the drug. A 3 per cent solution of procaine hydrochloride introduced in similar fashion had no effect except a lowering of the basal level 6 to 7 cm.

C. *Comparable Experiments on the Human Ureter.*—In 1 instance a ureter was obtained from a patient undergoing nephrectomy because of a malignant growth. Contractions of the longitudinal muscle shortened the specimen 6 to 7 per cent of its length every forty to fifty seconds, and the pressure curve was smooth at 8 cm. except for the spikelike rises to 25 to 30 cm. synchronous with the contractions of the longitudinal muscle. Active movement persisted almost five hours and was uninfluenced by the addition of 0.37 mg. of prostigmine methylsulfate or of 6 mg. of pilocarpine hydrochloride to the 180 cc. bath. One milligram of atropine sulfate slowed the rate of contraction somewhat,

24. Masson, P.: (*a*) Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, Am. J. Path. **4**:181, 1928; (*b*) Contribution to the Study of the Sympathetic Nerves of the Appendix: The Musculonervous Complex of the Submucosa, ibid. **6**:217, 1930.

25. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, Philadelphia, Lea & Febiger, 1928.

and 1:180,000 epinephrine hydrochloride caused slight shortening and a slight increase in rate of movement.

In 2 patients in whom nephrectomy was being performed a fine catheter was tied into the upper end of the remaining lower portion of the ureter, and studies were performed similar to those just described for the appendix. The catheter in each case was uneventfully withdrawn after a few days.

In each of these subjects the basal pressure was 6 to 8 cm. of water above the level of the ureter. In 1 (in whom the ureter was edematous and inflamed) there was a rise to approximately 20 cm. for a few seconds every five minutes; in the other, fine waves every three to five seconds were present, with peaks to 25 to 30 cm. of water every two to three minutes. Inhalation of amyl nitrite was without effect in either case, and subcutaneous injection of 0.67 cc. of a 1:1,000 solution of epinephrine hydrochloride subcutaneously also caused no change in either tracing except for an increase in the frequency of waves in the first subject. Twelve milligrams of morphine sulfate and one therapeutic ampule of prostigmine methylsulfate (0.5 mg.) were each without effect on the tracing of the second patient; but 1 cc. of solution of posterior pituitary of double the U. S. P. strength made the waves irregular, small and frequent, with some elevation of the basal level, and 10 mg. of acetylbetamethylcholine also rendered the peaks more frequent and elevated the basal level 2 to 3 cm. of water.

VII. CRITICAL REVIEW OF DATA ON THE ABSOLUTE RESISTANCE TO OUTFLOW (OF FLUID THROUGH THE APPENDIX INTO THE CECUM) AND ITS RELATION TO DISEASE OF THE APPENDIX

A. *Introduction.*—Reports on the correlation of the operative diagnosis with the absolute resistance to outflow (of fluid through the appendix into the cecum) determined at appendectomy have already been published,[26] and it has been indicated that the resistance is elevated, as a rule, in appendicitis. In order to control the determinations more rigidly, a series of readings has been correlated with the combined surgical and microscopic diagnosis, no case having been considered normal except those in which history, results of physical examination and operative and microscopic observations all were normal.

B. *Procedure.*—At the time of appendectomy a no. 19 needle was inserted into the distal lumen of the exposed appendix. The needle was connected by rubber tubing to an elevated flask of isotonic solution of sodium chloride fitted with a gravity drip bulb and adjusting valve

26. Wangensteen, Buirge, Dennis and Ritchie.[22] Wangensteen and Bowers.[2]

and with a manometer of fine bore. The flow of fluid was adjusted to a rate of 60 drops per minute, the fecal matter washing out of the appendix and into the cecum. The flow was then stopped, and the level above the appendix to which the manometer meniscus fell was termed the "absolute resistance to outflow."

C. *Evaluation of Variations in Resistance to Flow Introduced by Muscular Contractions During Determinations.*—In many instances it was necessary to divide the mesentery before insertion of the needle, and in others, especially with acutely inflamed specimens, the determination could not be made until after removal of the appendix. In 14 instances determinations were made before section of the mesentery and also afterward, or before and after amputation, or both. The mean arithmetic difference between values of water pressure before and after surgical intervention in this group was 9.7 cm., and in only 3 instances did it exceed 15 cm. The algebraic mean was 4.4 cm.

In several instances the length of the specimen as well as the change of resistance to flow with surgical intervention was determined in order to check the possibility that the change in resistance might be due to general contracture of the appendical musculature. There was no correlation between the changes in length and the changes in resistance to flow either with section of the mesentery or with amputation of the specimen. It therefore seems most likely that the variations are due to the incidental occurrence of the large tonus waves previously described, which are of adequate size easily to account for the discrepancies observed.

In confirmation of this conclusion, rhythmic variations in the resistance to outflow with fluid running at 60 drops per minute were commonly seen. The amplitude of these waves varied from 2 to 18 cm. of water pressure. The activity of the muscle even in the presence of the trauma necessarily inflicted was demonstrated also by faradic stimulation with a technic similar to that described elsewhere for experiments with apes [1b]; elevations of resistance from 43 to 68 cm. occurred in 1 case and from 34 to 76 cm. in another.

D. *Correlation of the Absolute Resistance to Outflow with the Clinicopathologic Diagnosis.*—The determinations for 70 specimens are presented in table 2. The mean resistance to outflow of 6 normal appendixes was 26 cm. of water. In 15 interval specimens the mean was 31.5 cm.; in 7 with fibrosis it was 54 cm., and in 8 shown microscopically to have residual inflammation it was 50 cm. In 11 appendixes showing minimal inflammation the mean was 68 cm. of water, and in 10 with more advanced inflammation it was 82.3 cm. In 13

specimens from the morgue, on the other hand, the resistance was insignificant, indicating the great importance of the muscular factor.

Inspection of the column of standard deviations from the mean of each group in table 2 shows that appendixes presenting a normal cytologic picture vary relatively little from a mean of about 30 cm., while the variability is greater in the acutely inflamed appendixes and most marked in the fibrosed interval specimens. The calculations of probable error show that the differences between normal and inflamed organs are statistically significant even in view of the variations due to large tonus waves.

TABLE 2.—*Correlation Between Present or Past Inflammation and Absolute Resistance to Outflow Determined in the Operating Room* *

Appendix	Number of Cases	Absolute Resistance to Outflow (Pressure Measured in Centimeters of Water)				
		Mean	Standard Deviation from Mean †	Probable Error from Mean †	Maximum	Minimum
Specimens from morgue	13	3	1.75	0.49	7	0
Normal	6	26	3.5	1.4	29	19
Interval specimens with normal cytologic picture	15	31.5	11.5	3.0	63	18
Interval specimens with fibrosis	7	53.6	48.0	18.1	120‡	0§
Interval specimens with some inflammation persisting	8	50	31.4	11.1	120‡	20
Minimally inflamed	11	68	36	10.9	120‡	20‖
"Acute suppurative"	10	82.3	36.3	11.5	120‡	30‖

* In the instances in which the absolute resistance to outflow was determined before and after section of the mesentery or amputation, the mean of the values obtained was used.

† Standard deviation $= \sqrt{\frac{1}{N}(M-V)^2}$. Probable error $= \frac{1}{N}\sqrt{(M-V)^2}$. In these formulas N stands for the number of cases, M for the mean and V for any individual value.

‡ As the apparatus used most of the time would record no higher than 120 cm., this value was assigned when no flow occurred at this level.

§ Narrowing throughout the lumen; the pressure was 80 cm. at 20 drops per minute.

‖ Postoperative determination: Some question exists as to whether amputation was at the true base or distal to the supposed obstruction.

VIII. EVALUATION OF THE ROLE OF NEUROMUSCULAR ACTIVITY IN INITIATING ACUTE APPENDICITIS

A. *Introduction.*—Wangensteen and I [1a] have shown that obstruction of the lumen of the normal human appendix results in elevation of the intraluminal pressure in the neighborhood of 80 to 120 cm. of water due to the secretion of fluid by the mucosa, with the development of ischemic necrosis and acute suppurative appendicitis. In the chimpanzee we have shown that this process, if not interrupted, will go on to gangrene and perforation.[1b] The importance of the muscular function will be established, therefore, if it can be shown to offer this degree of obstruction.

B. *Proof of the Existence of Cases of Acute Appendicitis with Spastic Obstruction to the Lumen.*—Appendixes each with an absolute resistance to outflow of 50 cm. of water or more in the operating room were subsequently fixed in 4 per cent solution of formaldehyde and sectioned longitudinally in search of organic obstructions. The observations are presented in table 3. It is evident that although organic obstruction was responsible wholly or in part for the elevation in resistance to outflow in 11 of 15 cases, in 4 cases it apparently played no part. In the 6 cases in which there was narrowing of the lumen a

TABLE 3.—*Evidence of Functional Obstruction: Absolute Resistance to Outflow Contrasted with Degree of Obstruction Visible on Longitudinal Section After Fixation in Formaldehyde Solution* *

	Absolute Resistance to Outflow (Pressure Measured in Centimeters of Water)		
	With No Obstruction Seen After Fixation	With Narrowing of Lumen Seen After Fixation	With Complete Obstruction Seen After Fixation
Acute suppurative appendicitis	100 cm.†	53 cm. 68 cm.‡ 110 cm. 110 cm.	124+ cm. 200 cm. 900 cm.§
Subsiding appendicitis	52 cm.	51 cm.‡ 112 cm.	
Interval specimen	63 cm.‖		
Interval specimens with fibrosis	.....	.....	77 cm.‖ 120+ cm.‖

* This table is limited to specimens showing an absolute resistance to outflow above 50 cm. of water. Each number represents the absolute resistance to outflow of one specimen in situ or within two minutes after amputation.

† This value was determined after amputation of the appendix and therefore cannot have been due to amputation distal to the site of obstruction.

‡ The narrowing was found only in the distal portion of the appendix, the inflammation throughout.

§ "Acute and chronic granuloma."

‖ The presence of elevated resistance to outflow in the absence of acute appendicitis will be discussed in section XII.

functional element must also have been present to cause a resistance to flow of the order of 50 cm. of water.

In order to show that these high values rest in fact on muscular action and not on an anatomic change overlooked on longitudinal section after fixation, evidence may be gathered from a comparison of the resistance to outflow of freshly excised appendixes with that of specimens studied after loss of tone in the muscle. In 32 unfibrosed specimens presenting varying degrees of inflammation, the mean resistance to outflow within a few minutes after removal from the patient was 45 cm. of water; more than a half-hour later the mean was 9 cm. It is evident, therefore, that at least 80 per cent of the resistance to

flow in this group was due to muscular activity; indeed, comparison with the values obtained from the specimens from the morgue (table 2) indicates that almost all the usual resistance is muscular in origin.

C. *Question of Physiologic Sphincter Action at the Base.*—It has already been reported that neither the mucosal folds around the appendicocecal orifice nor the muscular arrangement at the base of the appendix presents an anatomic basis for obstruction to the lumen,[22] but the possibility remains that the muscle in this region is capable of sphincter-like behavior.

A considerable number of appendixes was studied immediately after operation by incannulation of the tip and amputation of successive seg-

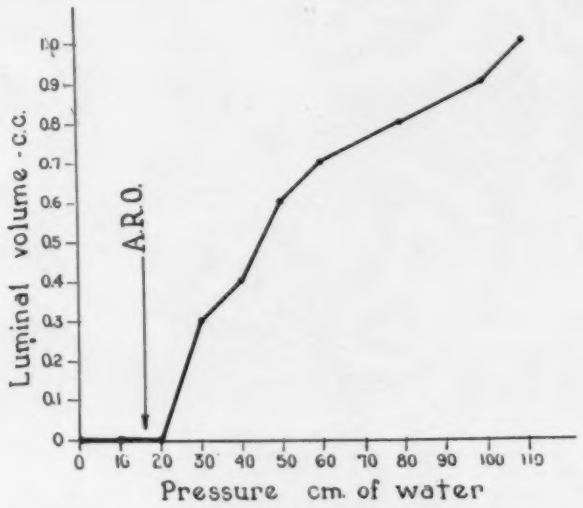

Fig. 7.—Graph made from data obtained from studies of an appendix in situ, illustrating the relation of the luminal volume to the intraluminal pressure. This volume uniformly remains zero in the normal appendix until the pressure is higher than the absolute resistance to outflow.

ments from the base to determine the effect on the resistance to outflow. By insertion of long, slender cannulas varying distances into the lumen of other fresh specimens, further information was obtained. In both types of experiment the appendix was found irritable, the resistance rising with each new manipulation. To test the full possible extent of such change, one specimen was excessively manipulated, and the resistance rose from 16 to 60 cm. in four minutes.

The most satisfactory method of approach to the problem proved to be determination of the luminal volume at varying levels of intraluminal pressure. For this purpose the tip of the appendix was incan-

nulated with a no. 19 needle; fluid was run through to empty the lumen of debris, and the resistance to outflow was determined. The base was clamped; the needle was connected to a capillary manometer on the one hand and to a 1 cc. tuberculin syringe on the other, and, with the volume characteristic of the manometer known, the intraluminal volume was determined at various pressures. To test whether the volume at atmospheric pressure was actually 0, aspiration with the needle was performed. The accuracy of the method was determined to be within about 0.05 cc.

The type of volume curve determined as the pressure was gradually raised was fairly characteristic. The volume remained 0 until the

TABLE 4.—*Luminal Volume at Pressures Corresponding to the Absolute Resistance to Outflow*

Time of Determination	Number of Cases	Diagnosis	Luminal Volume	Absolute Resistance to Outflow		
				Mean	Maximum	Minimum
In situ	2	Fibrosis	0	18	19	16
Specimens with Absolute Resistance to Outflow Volume Zero						
Immediately after removal	2	Normal	0	33	35	32
	2	Fibrosis	0	71	75	67
	1	Subacute	0	23	—	—
	3	Acute	0	88	200	29*
After being on ice	6	Normal	0	25	48	3
	2	Subacute	0	25	42	7
	9	Acute	0	24	77	8
Specimens with Absolute Resistance to Outflow Volume More than Zero						
Immediately after removal	1	Acute	0.1	30*	—	—
After being on ice	1	Interval specimen	0.05	35	—	—
	4	Acute	1.1	105	200†	8*

* No special effort was made to amputate the entire appendix including the appendicocecal junction, and the obstructed area was undoubtedly left behind in some cases, as Allen [41] suggested might occur.

† Complete organic obstruction at base.

pressure had been elevated sufficiently to overcome the tone of the muscle of the appendical wall; at this level there was regularly a rather sudden increase in volume of considerable degree. Thereafter each increment in pressure stretched the muscle a little more. A typical curve, determined before the appendix was removed at appendectomy, is illustrated in figure 7.

In 33 cases in which both the resistance to outflow and the luminal volume curves were determined, the volume at the pressure corresponding to the absolute resistance to outflow was 0 in 27, in none of which was the appendix more than minimally inflamed, and definitely more than 0 in 6, in 5 of which the appendix was acutely inflamed at the time of removal and in 1 of which it had been inflamed previously (table 4).

In each of the 27 specimens in which the volume was 0, each portion of the appendix must have resisted equally the tendency of the increasing intraluminal tension to spread the walls; each portion of the organ contributed a resistance equal to the resistance to flow of the appendix as a whole, and therefore there was no sphincter action at the base. That a segment which behaved as a sphincter might have been left behind is also unlikely, for in 2 instances the determinations were made during appendectomy and before division of either the mesentery or the base.

Of the 5 acutely inflamed appendixes showing a definite volume at the absolute resistance to outflow pressure, organic obstruction was evident in 2. One of the remainder presented a resistance of over 100 cm. when fresh and showed no evidence of obstruction on longitudinal section after fixation. Concerning the other 2, it is believed

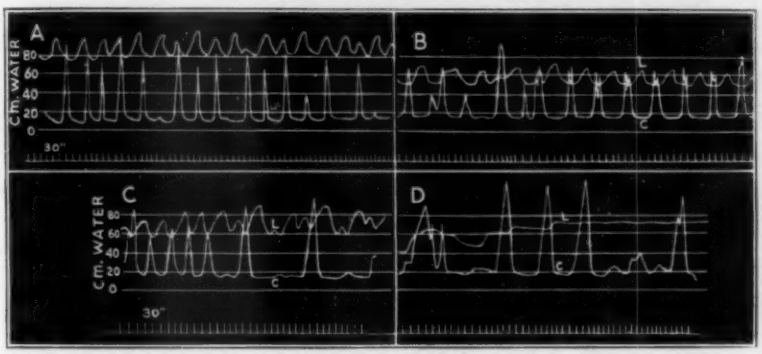

Fig. 8.—Kymographic records from four segments of an appendix studied individually in the water bath. The variations in rate of contraction are manifest: (*A*) distal segment, ninety-eight seconds; (*B*) second segment, seventy-five seconds; (*C*) third segment, eighty-six seconds, and (*D*) proximal segment, one hundred and ninety seconds. The segment next to the tip, therefore, had the fastest rate of rhythmic contractions. The appendix was an interval specimen without residual inflammation.

that amputation was performed distal to the obstruction. In the interval specimen the volume was at the limit of accuracy of the method.

D. *Data on the Gradient of Rates of Rhythmicity in the Appendix and the Relation to Acute Appendicitis.*—In order to determine whether a gradient of rates of rhythmicity occurs in the appendix similar to that described by Alvarez [6] for the ileum, chilled appendixes were cut into 2 to 5 equal segments, and each was mounted individually in the water bath. In 13 appendixes reasonable activity was observed, 7 of these being stimulated by addition of a 30 to 50 mg. crystal of barium chloride to the bath. The attempt to determine gradients was compli-

cated by the fact that in many specimens the rate became fast and feeble as the muscle failed, but an attempt was made to make calculations from each tracing at a point when full activity had been established and failure had not yet begun. Figure 8 illustrates the comparative activities of separate segments of an interval specimen.

If the site of fastest rhythmic contractions is correlated with the clinicopathologic diagnosis, a fairly consistent picture is obtained. In the only normal specimen of this series this site was at the tip; in 2 of the other 3 uninflamed specimens it was also in the distal half, while in 8 of the 9 specimens showing acute inflammation the segment showing fastest rhythmic contractions was either at the middle of the specimen (in 3) or in the proximal half. Unfortunately the absolute resistance to outflow of these appendixes was not determined in the operating room, but none showed organic obstruction. The suspicion arises, therefore, that hyperactivity in the proximal portion may have been a factor in initiating the acute inflammation in most of the cases. A large series of normal patients should be studied before conclusive results can be expected.

As has already been reported,[22] the propulsive activity of the appendix was studied in specimens made available by appendicostomy by insertion of pieces of bird shot, most of which passed in a few hours into the cecum. In several instances small amounts of feces were found on the appendicostomy dressings after the tip had been removed, in 1 instance in the same twenty-four hour period in which a shot was passing toward the cecum. It is evident, therefore, that such propulsive activity as is present is at times overcome or reversed.

IX. RELATION OF NEUROMUSCULAR ACTIVITY TO APPENDICAL PAIN AND THE EFFECT OF EPINEPHRINE ON IT

Most writers on appendical pain agree that the initial poorly localized pain is due to muscular tension in the appendical wall.[27] One school of thought ascribes the localized later pain to parietal peritoneal

27. (*a*) Alvarez, W. C.: Abdominal Pain: II. The Sensitive Regions in the Abdomen and Ways in Which They May Be Stimulated to Produce Pain, J. A. M. A. **102**:1351 (April 28) 1934. (*b*) Gray, S. H., and Heifetz, C. J.: Lymphoid Hyperplasia of the Appendix with a Note on Its Rôle in Acute Appendicitis, Arch. Surg. **35**:887 (Nov.) 1937. (*c*) McCloskey, B. J.: A Review of Certain Diseases of the Appendix Clinically Called Chronic Appendicitis: Physiology of Appendiceal Movements, Internat. Clin. **2**:101, 1937. (*d*) MacKenzie, J.: Symptoms and Their Interpretation, London, Shaw & Sons, 1920. (*e*) Morley, J.: Abdominal Pain as Exemplified in Acute Appendicitis, Brit. M. J. **1**:887, 1928. (*f*) Williams, O. T.: Abnormal Fat Assimilation Associated with Some Diseases of the Intestine, Biochem. J. **2**:395, 1906; (*g*) The Microchemical Change Occurring in Appendicitis, with a Note on the Incidence of the Disease in Various Countries, ibid. **3**:391, 1908.

involvement (McCloskey [27c] and Morley [27e]), and another to reference by reason of proximity of visceral and somatic sensory routes in the upper part of the lumbar region of the spinal cord (MacKenzie [27d]).

In subjects with an obstructed, extraperitonealized appendix [1a] pain is often experienced, sometimes in the umbilical region but usually in the right lower quadrant. In 1 case the pain in the right lower quadrant could be alternately reproduced and relieved by elevating and lowering the intraluminal tension.

Distention of the artificially obstructed appendix with saline solution, by means of a hypodermic needle inserted into the lumen at the time of appendectomy, was performed under local anesthesia four times.[28] In 1 instance a pressure of 170 cm. of water drew a complaint from the patient of "pain in the pit of the stomach"; higher pressures caused umbilical pain in 2 others, followed in 1 instance in three minutes by reference of pain to the right lower quadrant and in the other by pain in the right lower quadrant followed by nausea.

The type of bilateral pain in the lower part of the abdomen described by Wilkie [29] was seen in 1 patient with an unobstructed appendix made available by appendicostomy in whom crampy pains occurred in both lower quadrants during the passage of a bird shot through the lumen into the cecum. Two clinical patients with the same type of cramps proved to have a small concretion and an ingested piece of bird shot respectively in the appendical lumens.

Because of the action of epinephrine in relaxing the circular muscle of the appendix, 0.33 to 0.5 cc. doses of a 1 : 1,000 solution of epinephrine hydrochloride were injected subcutaneously into 9 patients with supposed acute appendicitis. Seven obtained complete or partial relief, and 2 did not. Of these 2, 1 proved to have acute suppurative appendicitis, and the symptoms in the other were subsequently shown to arise from ureteral obstruction. All those whose symptoms were relieved by the drug had appendical cause for their symptoms (table 5).[29a]

28. Dr. W. F. Bowers collaborated in the prosecution of these observations.

29. Wilkie, D. P. D.: Acute Appendicitis and Acute Appendicular Obstruction, Brit. M. J. **2**:959, 1914.

29a. Since submission of this paper for publication, placebos and epinephrine have been administered to a group of patients to try to obtain adequate control observations. The results indicate that some patients with other complaints obtain relief, as would be expected with intestinal spasm in some diarrheas. Some patients also failed to obtain relief in the presence of appendicitis (6 out of 22 patients). The series of administrations of placebo is too small to allow conclusions on a statistical basis, but the occasional case of acute suppurative appendicitis in the absence of organic obstruction in which almost complete relief was obtained from injections of epinephrine is very impressive.

Specimens from 7 of these 9 patients were sectioned longitudinally after fixation in solution of formaldehyde, and 4, from patients whose symptoms were partially relieved by the epinephrine, presented no narrowing of the lumen or obstructing fecalith.

X. CONTRIBUTION OF THE OBSTRUCTIVE THEORY OF APPENDICITIS TO THE EXPLANATION OF PERITONITIS IN CERTAIN CASES; DATA ON SEEPAGE THROUGH THE APPENDICAL WALL

In the course of intraluminal tension studies seepage through the appendical wall was often observed. In order to study the nature of

TABLE 5.—*The Effect of Epinephrine on Pain Due to Supposed Acute Appendicitis*

Patient	Age	Dose of Epinephrine Hydrochloride (1:1,000), Cc.	Pain Relief	Final Diagnosis	Status of Lumen of Fixed Specimen (Longitudinal Section)
1	25	0.50	Complete	Appendical colic	Lumen normal; shot-like fecaliths
2	28	0.50	Considerable	Appendix almost gangrenous	Stenosis and fecalith
3	16	0.50	Partial	Acute appendicitis; peritonitis	Not sectioned
4	19	0.33	Almost complete	Late subsiding appendicitis	Normal
5	13	0.33	Partial	Subsiding acute appendicitis	Normal
6	58	0.33	Partial	Mild acute appendicitis	Normal
7	18	0.33	Slight	Acute appendicitis	Not sectioned
8	12	0.33	None	Acute suppurative appendicitis	Narrowed at base
9	27	0.33	None	Mild acute appendicitis *	Small fecalith near tip; slight distension beyond

* Unaltered pain continued after appendectomy and was proved later to be due to ureteral colic.

this seepage more carefully, methylene blue solution was used, and the specimen was observed against a white background. Seven specimens were studied in the operating room immediately after amputation; the mean level of pressure at which seepage of fluid occurred was 92 cm. of water, the maximum 125 cm. and the minimum 60 cm. Seventeen others tested after being in the ice box gave similar results. In the usual case the seepage came from the general appendical wall and was colorless, but in a few cases in which the condition was acute the superficial vessels in some areas became engorged with the blue fluid and colored seepage occurred. In many cases the mesenteric lymphatics were also filled.

In 1 specimen, classified as showing "subsiding acute" appendicitis, the serosa was kept sterile after removal and during the determination

of the seepage level. Cultures of material taken from the surface after seepage had occurred at 100 cm. showed the presence of luminal organisms, in contrast to sterile control cultures prior to elevation of the pressure.

XI. RELATION OF INCREASED INTRALUMINAL TENSION TO RUPTURE

In order to determine the bursting strength of excised appendixes, 66 specimens were subjected to intraluminal pressures ranging up to 2,400 cm. of water (2.3 atmospheres). In 19 specimens this was not adequate to cause rupture; in 39 the pressure could not be raised this high because of rapid seepage, and in only 8, all presenting far advanced or gangrenous appendicitis, did rupture occur. In 1 gangrenous specimen this occurred at a pressure of 20 cm. of water. Maintenance of 1 atmosphere of pressure for ten days at room temperature also failed to rupture an uninflamed interval appendix. Preliminary incubation at 37 C. for one and three days respectively followed by submission to 2.3 atmospheres also failed to rupture 2 uninflamed appendixes.

XII. APPLICATION OF THE OBSERVATIONS ON NEUROMUSCULAR ACTIVITY TO THE GROSS AND MICROSCOPIC PATHOLOGIC OBSERVATIONS

A. *Comparison of the Clinicopathologic Diagnosis with the Degree of Luminal Obstruction Found on Longitudinal Section After Fixation in Solution of Formaldehyde.*—Review of the gross and microscopic observations on the appendixes used in this study throws some light on the difficulties involved in general application of the theory of the etiologic relation of luminal obstruction to acute appendicitis.

In 93 instances, comprising two series of consecutive cases, the specimens fixed in solution of formaldehyde were sectioned longitudinally in search of organic obstructions preliminary to the routine preparation of sections stained with hematoxylin and eosin for microscopic examination.

All gangrenous specimens showed complete obstruction of the lumen, as Wangensteen and Bowers [2] had found (fig. 9). Ten of 24 acutely inflamed specimens showed at least some degree of obstruction, and 2 showed partial obliteration of the distal lumen. The situation was similar in cases of mild appendicitis, while in the cases of subsiding appendicitis 20 out of 23 specimens showed no evidence of luminal obstruction. There were several cases, however, in which the degree of inflammation, as seen by both the surgeon and the microscopist, was mild or nonexistent and either complete obstruction or a high

degree of obstruction was evident (in several of these cases the resistance to outflow was found to be high).

B. *Demonstration of an Abnormal, Nonsecreting Mucosa in Minimally Inflamed or Uninflamed Appendixes with Complete Obstruction.*—In 6 cases of complete anatomic obstruction (black circles in figure 9) and in 5 cases of physiologic obstruction of marked degree, as indicated by a high resistance to outflow, microscopic studies were made, and in each instance the mucosal epithelium was found to be abnormal. In some instances it was entirely absent or entirely replaced by fibrous tissue, and in others a degree of subacute inflammation was evident with marked disruption of the secreting surface (fig. 10 *A*).

Demonstration of loss of secretory power in such circumstances is indicated by 1 case in which appendicostomy was done and in which

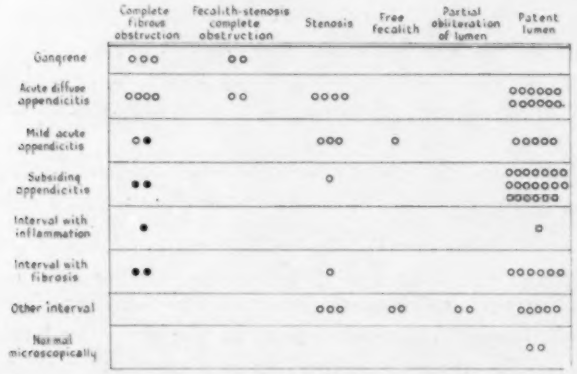

Fig. 9.—Graph showing the correlation between the patency of the lumen of the human appendix, as determined by longitudinal section after fixation in solution of formaldehyde, and the clinicopathologic diagnosis. The black circles indicate persons with abnormal mucosa (see text and figure 10 *A*).

unsuspected stenosis was present proximally. Acute appendicitis, proved by microscopic study of the amputated tip, developed with the appendix in the new site and was completely relieved by drainage of the distal lumen. No evidence of fluid secretion could be demonstrated by either the collection or the manometric method.[30] After the patient was dismissed from the hospital, however, secretion recommenced, and the appendix was removed seven months later for this reason; the distal mucosa now was normal in appearance (fig. 10 *B*); the recovery was comparable to that seen in the rabbit after relief of obstruction.[31]

30. Wangensteen, Buirge, Dennis and Ritchie.[22] Wangensteen and Dennis.[18]

31. Buirge, R. E.; Dennis, C.; Varco, R. L., and Wangensteen, O. H.: Histology of Experimental Appendical Obstruction (Rabbit, Ape and Man). Arch. Path. **30**:481 (Aug.) 1940.

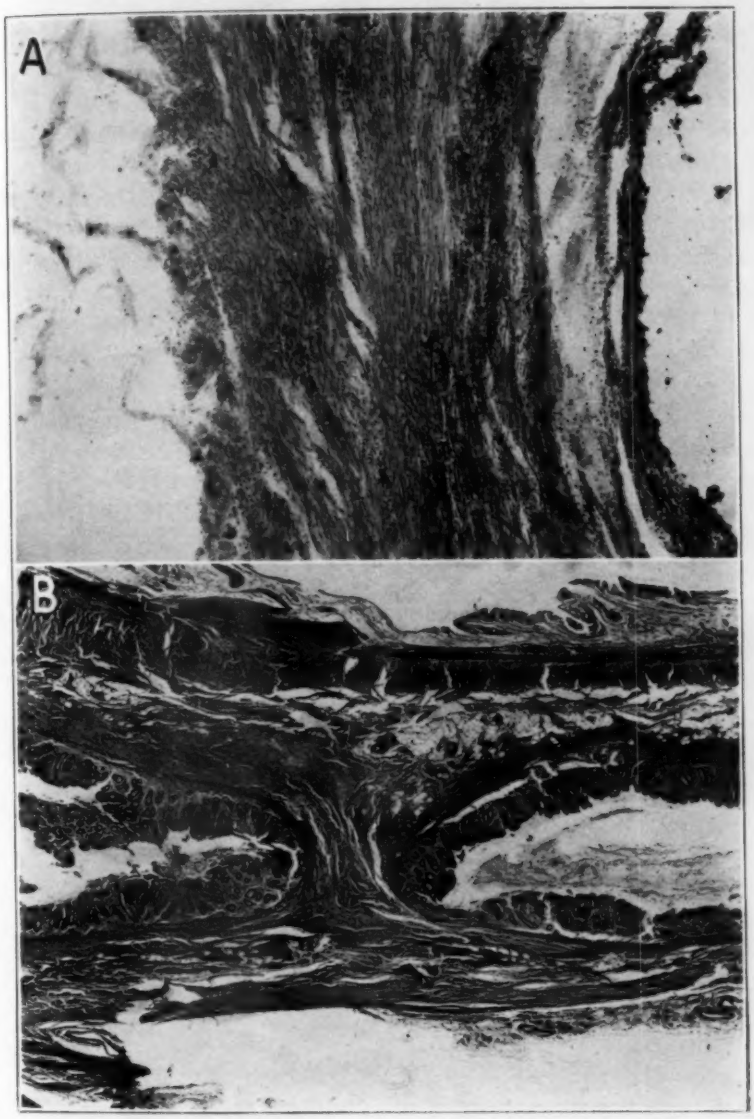

Fig. 10.—Photomicrographs. *A*, marked abnormality of the mucosa distal to a complete obstruction. Subsiding inflammation is present. Both the epithelium and the glands have been lost. (Hematoxylin and eosin stain; × 60.) *B*, an appendix removed seven months after appendicostomy. In the first few days after appendicostomy acute appendicitis developed and was relieved by drainage of the distal lumen; the resistance to flow eight hours later was 85 cm. of water, and roentgen ray examination with the aid of iodized poppyseed oil showed an area of stenosis in the proximal portion of the appendix; obstruction was therefore incomplete. Complete fibrous obstruction developed in the intervening months, and normal mucosa is present distally (at the right). (Azocarmine stain; × 10.)

C. *Development of Complete Organic Obstruction Following Acute Appendicitis.*—In the case mentioned in the preceding paragraph, roentgenologic study with iodized poppyseed oil a few days after amputation of the tip of the appendix for relief of appendicitis showed two marked constrictions near the base, but the resistance to flow at that time was below 100 cm. of water pressure. When the specimen was removed seven months later, the obstruction was physiologically and anatomically complete (figure 10 *B*). It is suggested but not conclusively proved that the inflammatory reaction led directly to additional fibrosis and complete obstruction.

D. *Acutely Inflamed Appendixes Presenting No Anatomic Obstruction.*—As figure 9 indicates, 38 specimens presented a greater or less degree of active or subsiding appendicitis with no obstruction demonstrable on longitudinal section after fixation in solution of formaldehyde. Although it is possible that evidence of stenosis would have been found more often if the appendixes had been opened in the fresh state, as Williams and Boggon recommended,[32] the presumed obstructive factor in these specimens must have rested primarily on the functional basis previously shown to exist.

E. *The Relation of Luminal Content to Luminal Volume and Diagnosis.*—In 24 specimens the luminal content of the chilled specimen was expressed and weighed. The appendix was thereafter incannulated and brought to body temperature for determination of the volume at 20 cm. of water pressure. No correlation was found between the magnitude of the luminal content and either the pathologic condition of the specimen or the volume at 20 cm. of water pressure, with the reservation that the only 3 specimens containing more than 0.5 Gm. of material had a luminal volume of over 0.5 cc. at 20 cm. In this group of 24 specimens, the 10 with a definite luminal volume at 20 cm. of water pressure were acutely inflamed.

PART 3. INTEGRATION OF OBSERVATIONS

XIV. COMMENT

A substantial part of the argument of Aschoff and his associates concerning the origin of appendicitis rests on stasis secondary to the supposed lack of active movements of the organ (Aschoff and Pokerny [7a] and Ruf [71]). The present study demonstrates active movements in over 90 per cent of normal specimens after excision and also marked activity in appendicostomy preparations, in reference both to changes in resistance to flow of fluid and to active propulsion of foreign bodies. As the present

32. Williams, B. W., and Boggon, R. H.: The Mechanics of Appendicitis, Lancet **1**:9, 1934.

series is apparently larger than any heretofore reported, the activity of the organ seems well established, and the tenet that stasis is an important factor in the causation of appendicitis is rendered untenable.

Certain differences between the recorded movements of the appendix in situ and after excision exist. With excision the large tonus waves disappear, and certain influences must therefore have been exerted, either nervous or vascular, on the appendix in situ.

The responses to the administration of drugs throw some light on the factors involved in the resistance to flow offered by contractions of the circular muscle of the appendix. In the first place, the slight elevation of the basal level of resistance during spinal anesthesia indicates that the tonus of the appendical circular muscle must be either intrinsic in nature or dependent on some extraspinal reflex. That the former is the case is indicated by the fact that although the level of the resistance to flow is only a fraction as high in the specimens studied in the water bath as in those made available by appendicostomy, it is unchanged immediately after removal of the appendix in the operating room. It follows that the low resistance encountered in the water bath is lower than in situ because of impaired nutrition.

The instillation of cocaine into the lumen of an appendix made available by appendicostomy resulted in elevation of the peak levels of pressure, which must have been due to diffusion of the drug to the muscle itself, yet the nature of the circular muscular activity was not otherwise altered. Meissner's plexus, past which the cocaine must have diffused and which must have been exposed to a concentration of the drug at least equal to that in the muscle, therefore (1) must not be essential to the movements of the muscle, (2) must exert an inhibitory influence on tone or (3) must be insensitive to the drug.

On the whole, the responses of the appendix to a variety of drugs suggest that the mechanisms involved in those responses must be similar to those of the ileum; but with amphetamine and with morphine a qualitative difference is demonstrable, and with pilocarpine and with atropine much greater sensitivity was found in the appendix than has been reported for the ileum.

With regard to pain, localization in the right lower quadrant following a rise in intraluminal pressure, whether that rise occurs spontaneously in extraperitonealized artificially obstructed appendixes or is induced at appendectomy under local anesthesia, indicates that parietal peritoneal involvement is not always requisite to reference of pain. Bilateral colic in the lower part of the abdomen has been proved due to the presence of a foreign body in the appendical lumen in 3 cases. Occurrence of this type of pain, attributed by Wilkie to "obstructive appendicitis," during the passage of a shot through the lumen of an appendix made available by appendicostomy suggests that the pain is due to contractions

on the foreign body rather than to obstruction of the lumen. The relief of pain by the injection of epinephrine indicates that muscular contraction or spasm is in part, at least, responsible for the pain. Failure of partial relief of pain after the subcutaneous injection of an adequate amount of epinephrine might be expected to indicate that the origin of the pain is not appendical but might well be renal.

It has been shown elsewhere that, in contrast to other animals,[33] man, the chimpanzee and the rabbit [34] possess an appendix with mucosa which secretes fluid and is therefore capable of elevating intraluminal tension if obstruction to the lumen occurs.

It has been shown earlier in the paper that there is a high degree of correlation between absolute resistance to outflow in the fresh state and the diagnosis based on clinicopathologic observations. On the other hand, the correlation between stenosis evident on section of fixed specimens and resistance to outflow or clinicopathologic diagnosis is less evident.

A small group of acutely inflamed appendixes has been presented (table 3) in which obstruction was demonstrable by elevation of resistance to outflow in the fresh state but not on longitudinal section after fixation in solution of formaldehyde. In 1 of these there was a definite luminal volume at the resistance to outflow pressure, which was 100 cm. of water, and yet no obstruction showed after fixation (section VIII, subsection C), indicating localized functional obstruction. For this reason the thesis is advanced that a functional mechanism of obstruction may occur in appendicitis. The rhythmic nature of the variations to flow in normal and in inflamed specimens in situ, immediately after removal and in the water bath, together with the elevation in resistance to flow by faradic stimulation in situ, indicates that this functional factor is muscular. Earlier proof that obstruction leads to microscopically typical appendicitis in the rabbit, the ape and man [35] suggests that muscular obstruction may play an etiologic role in clinical appendicitis, but until such a course of events can be instituted experimentally in man, the efficacy of spastic obstruction in producing the disease cannot be conclusively proved. Certain indirect evidence is at hand, however, for pain which could be at least partially relieved by epinephrine was present

33. Dennis, C.; Buirge, R. E., and Wangensteen, O. H.: An Inquiry into the Functional Capacity of the Cecal Appendage in Representative Birds and Mammals, Surgery **7**:372, 1940.

34. (a) Dennis, C.; Buirge, R. E.; Varco, R. L., and Wangensteen, O. H.: Studies in the Etiology of Acute Appendicitis: An Inquiry into the Factors Involved in the Development of Acute Appendicitis Following Experimental Obstruction of the Appendical Lumen of the Rabbit, Arch. Surg. **40**:929 (May) 1940. (*b*) Wangensteen and Dennis.[1]

35. Footnotes 31 and 34.

in 4 cases of appendicitis in which longitudinal section of the fixed specimen showed no narrowing of the lumen (table 5), and with the exception of relaxation of smooth muscle, no mechanism by which this drug can relieve pain has come to my attention. It therefore follows that increased tension must have been present, which could not have been the case without obstruction to the lumen, due necessarily in this group of cases to spasm.

In a recent publication Koster and Shapiro [36] reported a series of determinations of "initial resistance to luminal perfusion pressure" in appendixes in situ at appendectomy and postoperatively. They found no correlation between the levels of resistance and the pathologic (microscopic) diagnosis. The discrepancy between their results and those herein reported may be due to (1) some differences in technic, (2) undue delay after section of the mesoappendix and base of the appendix, a time interval not specified by them but shown to be of great importance in the present paper, and (3) classification of their cases on the basis of microscopic observations alone. Classification of the cases presented in table 2 on the basis of microscopic observations alone robs the data of much of their significance. The possibility of return to normal cytologic conditions after conservative management of clinically diagnosed appendicitis is indicated by the finding of no evidence of active inflammation in 45 of the 68 interval specimens in this series, and yet most of those specimens had an elevated resistance to outflow. In addition, symptoms relievable by appendectomy despite normal gross and microscopic observations were encountered in 10 of 15 cases considered clinically to be of acute appendicitis, results comparable to those of Rea and Kleinsasser [37] and C. W. Mayo.[38] It has already been pointed out that in the early stages of the disease there may not be microscopic evidence of inflammation.[16] It is therefore evident that disease of the appendix cannot be diagnosed by the microscopic observation of acute inflammation alone.

Koster and Shapiro in addition accused Wangensteen and me [16] of presenting insufficient microscopic data to prove the dependence of acute appendicitis in our human subjects on luminal obstruction. Van Zwalenburg [39] demonstrated in 1904 that artificially increased intracecal pressure

36. Koster, H., and Shapiro, A.: Role of Intraluminal Obstruction in the Pathogenesis of Acute Appendicitis, Arch. Surg. **41**:1251 (Nov.) 1940.

37. Rea, C. E., and Kleinsasser, L.: End Results Following the Removal of an "Inactive" Appendix, Surgery **4**:179, 1938.

38. Mayo, C. W.: Exploration of the Abdomen and Appendectomy for Atypical Symptoms: Results Five Years After Operation in One Hundred Cases, West. J. Surg. **42**:189, 1934.

39. Van Zwalenburg, C. V.: Obstruction and Consequent Distention: The Cause of Appendicitis as Proved by Cases and by Experimental Appendicitis in Dogs, J. A. M. A. **42**:820 (March 26) 1904.

in the dog leads to acute inflammatory changes in the wall. The microscopic data from the ape and rabbit experiments,[35] which Koster and Shapiro failed to mention, showed clearly the relation of the development of increased intraluminal tension to the development of the classic microscopic picture of acute appendicitis. Aside from the few microscopic data presented, therefore, the demonstration of increasing intraluminal tension in obstructed human appendixes with intact mucosa is powerful evidence that obstruction in such organs leads directly to acute appendicitis.

The early changes of mucosal injury following sustained moderate elevation of intraluminal tension were observed by us in the rabbit.[34a] In this species a pressure of less than 20 cm. of water maintained for twenty-four hours resulted in edema and disorganization of the mucosa, combined with diminished secretory capacity. More prolonged periods or more elevated pressures resulted in more marked changes, particularly in the development of acute inflammation. The findings in the human specimens presenting complete obstruction indicate that in man also the mucosa must be sensitive to prolonged increases in pressure and that the rate of secretion slows after the prolonged elevation of pressure due to some types of obstruction.

In the rabbit it was possible to relieve the obstructing mechanism, and the microscopic picture was found to return to normal in the course of a few hours.[31] Similar mucosal recovery, as far as microscopic criteria are concerned, was observed in the case of an obstructed extraperitonealized appendix in which free drainage onto the abdominal wall persisted after relief of an acute attack by amputation of the tip. The return of actual secretory function is testified by an obstructed, extraperitonealized appendix in which the external fistula closed spontaneously with resultant and clinically typical appendicitis, cured by spontaneous reopening of the fistula.

If the facts found in this investigation are followed to their logical conclusion, the question whether an appendix in the early stages of acute appendicitis will become gangrenous and rupture, will subside spontaneously or will form a mucocele must depend on several factors. If the obstruction is complete and the mucosa actively secreting, then gangrene may be anticipated; but if the obstruction is spastic and therefore may be expected to allow escape of fluid at not too high a pressure, gangrene probably would not occur, for the mucosal injury produced by the sustained moderate pressure would inhibit further secretion after a time, and the process should then subside. If an appendix with already inhibited mucosa of such type should become completely obstructed, secretion might be expected to cease before rupture occurred, and mucocele should result.

It has been reported in previous papers that there is obstruction in most cases of appendicitis and that the disease may be experimentally produced by ligature obstruction in those species in which the organ secretes fluid.[40] In the preceding pages evidence has been presented that in certain cases the condition rests on obstruction of a muscular or functional nature rather than on organic occlusion and that organic obstruction may be the result of previous milder degrees of inflammation. It is evident, therefore, that early mild attacks of the disease may be followed by attacks of increasing severity as the degree of organic obstruction increases, terminating in an attack with complete obstruction and gangrene or, less often, mucocele.

XV. CONCLUSIONS

1. Under proper conditions the excised surviving normal human appendix is capable of active rhythmic contractions of both circular and longitudinal layers of muscle. Inflamed specimens contract less well.

2. The resistance to flow of fluid through the lumen of the normal appendix in situ is due primarily to tonus of the circular muscle, and rhythmic contractions of that muscle vary the resistance to flow.

3. The absolute resistance to flow of fluid offered by an incannulated normal appendix in situ is identical with the normal intraluminal tension. This is usually 15 to 30 cm. of water pressure, while that in the cecum is 2 to 5 cm.

4. At such pressures the normal human appendix has a luminal volume of less than 0.05 cc. There is no sphincter or sphincter-like action in the proximal as distinguished from the distal portion. A luminal volume greater than 0.05 cc. determined by the method described indicates a pathologic state.

5. Epinephrine relaxes the appendical but not the ureteral musculature.

6. Morphine and amphetamine produce responses in the appendix qualitatively different from those in the ileum, and pilocarpine and atropine show quantitative differences. The behavior of the appendix after administration of a variety of other drugs was found similar to that known for the ileum.

7. Inflamed appendixes present an average resistance to outflow (of fluid through the appendix into the cecum) three times normal, and that of interval specimens usually falls between.

8. Evidence is presented that acute suppurative appendicitis but not gangrene may be initiated by spasm of a portion of the muscular wall of the appendix. The stimulus for this spasm is not known.

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40. Footnotes 22, 31 and 34.

9. Appendical pain, including the pain radiating to the right lower quadrant, is largely due to tension on the muscular wall of the organ and may usually be ameliorated by epinephrine.

10. Seepage of infected fluid through the appendical wall occurs at levels of intraluminal tension commonly reached in appendicitis. A ready explanation of many cases of peritonitis without rupture, such as those stressed by Allen,[41] is therefore at hand.

11. Rupture during appendicitis is due to digestion of the wall, and the normal appendical wall can withstand an intraluminal tension of over 2 atmospheres.

12. Completely obstructed appendixes may remain uninflamed because of loss of secretory power of the mucosa. Associated microscopic changes are present.

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41. Allen, R. B.: An Analysis of Certain Clinicopathologic Features of Disease of the Appendix, Journal-Lancet **52**:614, 1932.

LYMPHOSARCOMA OF THE PROSTATE GLAND

WITH REPORT OF A CASE

WILLIAM KAUFMANN, M.D.
AND
ARTHUR W. WRIGHT, M.D.
ALBANY, N. Y.

Among primary malignant prostatic tumors, those of lymphoid origin are considered to be extremely rare. To date, however, a fair number of cases of so-called primary lymphosarcoma of the prostate gland have been reported, but the great majority of them have been discarded by recent investigators on the ground that insufficient clinical or histologic evidence was presented to justify the diagnosis. Since carcinoma is the most frequent type of primary malignant tumor of the prostate gland and since many of these prostatic new growths may be composed of primitive, highly undifferentiated cells, a majority of the tumors reported as lymphosarcoma have been looked on as highly anaplastic carcinoma which was called lymphosarcoma by mistake. A strong point in favor of the rarity of lymphosarcoma in this organ is the absolute paucity, not to say absence, of lymphoid tissue from which primary lymphosarcoma could arise. We shall come back to this point later and discuss its relative value in the diagnosis of prostatic tumors. For many investigators this argument is sufficient reason for excluding lymphosarcoma from the list of the possible types of primary malignant tumor of the prostate.

Symmers [1] claimed that only 1 reported case of primary prostatic lymphosarcoma, that of Coupland,[2] could be accepted without question.

Coupland's patient was a 29 year old man who four years previously had suffered from acute gonorrhea complicated by orchitis and a syphilitic chancre. When the patient came to autopsy, two months after the first observation of symptoms, a fleshy prostatic tumor, 20.3 cm. in circumference and 8.9 cm. in length, was found. The new growth had surrounded the neck of the bladder and the prostatic urethra, had invaded the base of the bladder in the region of the median lobe and had metastasized to the pancreas and the right adrenal gland.

From the Department of Pathology and Bacteriology, Albany Medical College and the Laboratories of the Albany Hospital.

1. Symmers, D.: Primary Lymphosarcoma of the Prostate, Arch. Surg. **6**:755-763 (May) 1923.

2. Coupland, S.: Lymphoma (Lymphosarcoma) of the Prostate: Secondary Nodules in Pancreas and Supra-Renal Capsule, Tr. Path. Soc. London **28**:179-185, 1877.

Symmers himself studied 1 case at Bellevue Hospital in New York, that of a 30 year old man, whose clinical history and pathologic findings were almost identical with those of Coupland's patient. He felt that such tumors "are not so rare as the literature would indicate." He subsequently ventured the opinion that lymphosarcoma should always be considered a possibility in patients under 35 years of age who suffer from prostatic hypertrophy.

In the opinion of Ferguson and Stewart,[3] Symmers' case and 3 reported prior to it can be accepted as cases of primary lymphosarcoma of the prostate gland. One of the 3 was Coupland's case. The second was that described by E. Kaufmann.[4]

The patient was a 24 year old aniline worker. The tumor had apparently arisen around the trigone of the bladder and, besides infiltrating the urethra and the right seminal vesicle, had metastasized to the pleurae, kidneys, pancreas, dura mater, cervical lymph nodes, tibia, calvarium and one small lymph node in the pelvis. Histologically, the neoplasm was diagnosed as lymphosarcoma. It was composed of small lymphoid cells, embedded in a finely reticular stroma.

Although Ferguson and Stewart accepted the diagnosis of lymphosarcoma in this case, the evidence presented was not satisfactory to Ewing. The third case was that of a 41 year old farmer, reported by Quinby,[5] in which a diagnosis of lymphosarcoma of the prostate gland was made by biopsy. This patient became rapidly emaciated and died five months after the onset of the first symptoms, with generalized metastases. Autopsy was not done.

Ferguson and Stewart themselves presented a fifth case which was accepted by the Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists as "true lymphosarcoma."

This new growth involved the prostate gland, bladder and seminal vesicles and metastasized to the pelvic, aortic, abdominal and inguinal lymph nodes and to both kidneys. It occurred in a 36 year old white man, who thirteen years before his present illness had suffered from gonorrhea with marked posterior urethritis. Six months prior to his admission to the hospital he had lost 30 pounds (13.5 Kg.) in weight. For the last seven weeks of this period nocturia with increasing frequency but without burning, tenesmus or hematuria was the main symptom. One week before admission he had an attack of acute urinary retention. The blood chemical findings were within normal limits, but the urine showed albumin and a large amount of pus. An operation was performed, and the specimen removed was reported as carcinoma. When the patient was referred to the Memorial Hospital for the Treatment of Cancer and Allied Diseases, in New York,

3. Ferguson, R. S., and Stewart, F. W.: Lymphosarcoma of the Prostate, J. Urol. **28**:93-104, 1932.

4. Kaufmann, E., in Socin, A., and Burckhardt, E.: Die Verletzungen und Krankheiten der Prostata, in Billroth, T., and Luecke, G.: Deutsche Chirurgie, Stuttgart, Ferdinand Enke, 1902, no. 53, pp. 394-395.

5. Quinby, W. C.: Lymphoblastoma (Lymphosarcoma) of the Prostate, J. Urol. **4**:137-144, 1920.

rectal examination disclosed a hard irregular tumor, 4.5 cm. wide, situated between and around the seminal vesicles. It was impossible to treat the new growth effectively, and it increased rapidly in size. The patient died two months after his admission to the hospital. Autopsy disclosed lymphosarcoma of the prostate gland.

Since these publications of Symmers and Ferguson and Stewart, other cases of lymphosarcoma of the prostate gland have been reported. Of these, those reported by Mason,[6] Cole and Martin,[7] Rathbun and deVeer[8] and Smith[9] have all been cases which we believe can be accepted as cases of definite prostatic lymphosarcoma. Some of the tumors occurred in patients much older than those of Symmers and Ferguson and Stewart. Cole and Martin's patient, for example, was a 56 year old man and Rathbun and deVeer's a man of 52. The duration of the disease seemed to vary between three and nine months. In all reported cases the growth was a rapidly progressing one, infiltrating diffusely the surrounding structures and producing widespread lymphatic metastases. In all cases the growth was fatal despite a variety of therapeutic measures.

Another case, although not one of a malignant tumor, might be included in this series, particularly because of its peculiar histologic aspect. The tumor occurred in a 68 year old man and was diagnosed as lymphoma of the prostate gland. The case was reported by Wegelin.[10]

The patient had an indefinite history of gastrointestinal disorders with marked prostatic hypertrophy of two months' duration. The prostate gland was found to be of the size of an apple, and cystoscopic examination showed it to protrude markedly into the bladder. Perineal prostatectomy was done, and an encapsulated tumor measuring 5.5 by 4.5 by 3 cm. and weighing between 50 and 60 Gm. was removed from the right side of the gland. The left lobe of the prostate appeared perfectly normal. After initial improvement septicemia suddenly developed, and the man died twenty days after the operation. No autopsy was done.

Histologically, the neoplasm was found to consist for the greater part of fully mature, round, follicle-like lymphatic tissue, the follicles ranging from 0.5 to 1.5 mm. in diameter. Often these follicles were closely packed and formed large conglomerates of lymphatic cells. Germinal centers were absent. The lymphatic tissue was indistinctly separated from the ground substance of the tumor, which consisted of smooth muscle tissue. The muscle tissue throughout the entire tumor was diffusely infiltrated with lymphocytes. The lack of glandular tissue in the neoplasm and the appearance of the encapsulated muscle fibers led Wegelin to diagnose lymphoma arising in an encapsulated myoma of the prostate gland.

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6. Mason, D. G.: Primary Malignant Lymphocytoma of the Prostate Gland, Arch. Path. **16**:803-808 (Dec.) 1933.

7. Cole, F. H., and Martin, L. R.: Lymphosarcoma of the Prostate, J. Urol. **31**:803-811, 1934.

8. Rathbun, N. P., and deVeer, J. A.: Lymphosarcoma of the Prostate, J. Mt. Sinai Hosp. **4**:771-780, 1938.

9. Smith, L. D.: Lymphosarcoma of the Prostate, J. Urol. **38**:375-382, 1937.

10. Wegelin, C.: Ueber ein Lymphom der Prostata, Wien. klin. Wchnschr. **48**:1236-1237, 1935.

Recently we have had an opportunity in this laboratory to study a case of lymphosarcoma of the prostate gland. This case is now reported in detail.

REPORT OF A CASE

A man 62 years old was admitted to a hospital on May 9, 1939, complaining of burning urination for the previous two or three years and of frequency of urination and nocturia for seven weeks. Pain low in the abdomen accompanied urination. His last normal micturition had occurred two days previously. Since then he had urinated by dribbling only. Except for chronic constipation his past history was not pertinent. On physical examination the lower part of the abdomen was tender and the bladder distended. Rectal investigation revealed a hard, enlarged and tender prostate gland. The urine at this time contained albumin (2+), many red blood cells and neutrophils. The erythrocyte and leukocyte counts were within normal limits. The blood chemical findings were reported as within normal range. The Wassermann test was negative.

On May 15 suprapubic prostatectomy, cystotomy and bilateral vasectomy were done. The material submitted for examination consisted of several irregular pieces of firm grayish white tissue. The amount received indicated that the gland was moderately enlarged. On histologic examination the organ was found to be diffusely invaded by a new growth, which was considered to be lymphoblastoma. Six days after the operation pneumonia developed, but the patient recovered and was discharged on June 10, at which date the suprapubic wound was entirely healed. No urinary difficulties were noticed.

On July 2, approximately seven weeks after the first operation, the patient again appeared complaining of severe pains in the bladder region, especially about the operative scar. Between the time of his first admission to a hospital and this date, he had had about 10 treatments with roentgen rays of high voltage. Examination now revealed a hard, large, irregular mass in the region of the bladder. Inguinal lymph nodes, however, were not palpable.

The patient was transferred to the Albany Hospital on July 24. At this time a large hard tumor, lying directly beneath the skin above the symphysis pubis in the midabdominal line, was noted. The lower end of the suprapubic scar of the previous operation was ulcerated and contained a sinus, through which urine leaked. There were also small pink nodules in the suprapubic wound. On rectal examination an extremely large prostatic tumor, beyond which the exploring finger could not be passed, was found. At this time the inguinal lymph nodes were greatly enlarged, some measuring 3 cm. in length. The next day suprapubic irrigation of the bladder was performed. This procedure was painful and yielded a large amount of purulent material.

The same day biopsy of the subcutaneous tumor showed extensive diffuse infiltration of the stratum corium and the stratum subcutaneum by a rapidly growing, highly malignant, widely infiltrating neoplasm. In general the cells which formed the new growth were quite uniform in size. They appeared approximately round or oval, sometimes polyhedral, and contained scanty, finely granular, faintly basophilic cytoplasm with extremely faint cell membranes. The nuclei were large, vesicular, irregularly round or oval, had distinct nuclear membranes and contained small numbers of minute, deeply stained chromatin granules which stood out sharply in a finely reticulated pale blue nucleoplasm. Mitotic figures in all phases were present in abundance. Giant and multinucleated cells were not observed.

The arrangement of the neoplastic cells was worthy of note. Usually they formed chainlike strands from one to several cells thick, which infiltrated and separated the collagenous strands of the subepithelial tissues. One gained the impression that this chainlike or cordlike arrangement was not the result of an inherent tendency on the part of the cells to grow in this fashion but rather the result of the invasion of natural tissue planes. Often the cells in any given strandlike mass overlapped, seeming to form elongated and distinct entities.

Sometimes, especially when the tumor invaded the looser tissues of the stratum subcutaneum, the chainlike or cordlike arrangement of the cells was less frequently

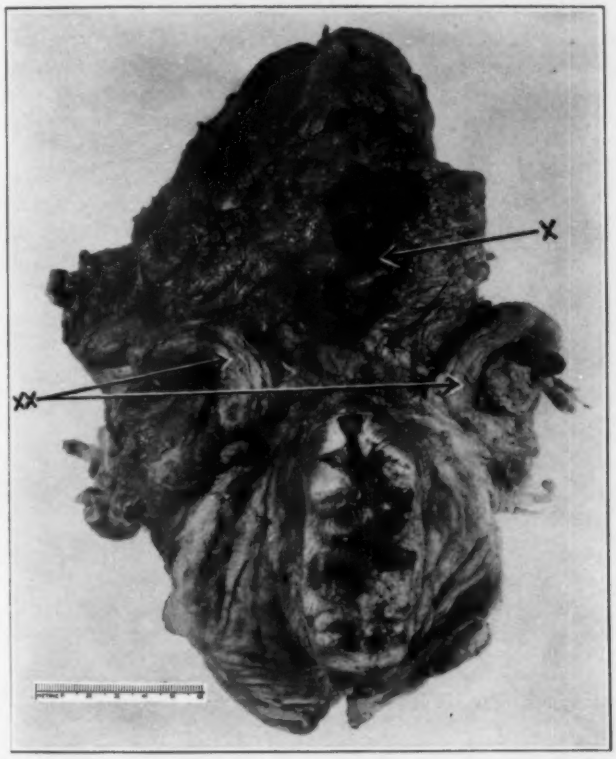

Fig. 1.—The entire tumor mass involving the skin and the bladder. *X* indicates the bladder; *XX*, the deferent ducts. For detailed description see the text.

noted. Here the neoplastic growth was more diffuse, and the individual cells appeared quite closely packed together, being separated only occasionally by delicate strands of collagen fibrils. These fibrils were considered to be part of the preexistent stroma.

In one section lymphatics of the subepithelial portion of the stratum corium were dilated and contained neoplastic cells. Here the cells appeared as separate entities, often closely packed, but sometimes occurring singly. Under these conditions the cytoplasm was more readily seen and the nucleus appeared even more vesicular than elsewhere. The cells sometimes resembled atypical monocytes.

Moderate numbers of tumor cells showed degenerative changes, which varied from early pyknosis and karyorrhexis to complete disintegration of some cells. Occasional eosinophils were found within the tumor tissue.

On the basis of these observations a diagnosis of lymphoblastoma was made by a member of this department. In view of the fact that intensive treatment with high voltage roentgen rays failed not only to affect the tumor but even to prevent further growth and enlargement, the sections were reexamined by one of us (A. W. W.). It was felt that in spite of the anaplastic lymphoblastomatous character of the growth the cells in some situations appeared more like epithelial cells than like lymphoblasts. Indeed, the cordlike arrangement, which in some places was pronounced, the occasional tendency of some of the cells to form crude alveolus-like structures and the clinical history of primary prostatic origin led to the conclusion that the new growth was a highly anaplastic, radioresistant carcinoma of prostatic origin. As such the new growth was reported to the tumor clinic.

Fig. 2.—Low power view of right hypogastric artery and vein surrounded partially by tumor tissue.

The urine at this time was cloudy, with a specific gravity of 1.020 and with a neutral reaction; it contained albumin (2+) but no sugar. Great numbers of pus cells were present. The erythrocyte count was 3,400,000, with hemoglobin 74 per cent of normal. There were 9,700 leukocytes per cubic millimeter, with 81 per cent neutrophils, 1 per cent eosinophils, 10 per cent lymphocytes and 6 per cent monocytes. The blood sugar was 84.7 mg. per hundred cubic centimeters; the nonprotein nitrogen, 31.4 mg., and creatinine, 1.15 mg. The temperature varied between 98 and 101 F.

On July 27 roentgenograms of the pelvis did not show any bone metastases. On August 4 the entire skeleton was examined roentgenographically and no evidence of tumor involvement could be found. The lungs also were free from metastases. On July 29 treatment with roentgen rays of high voltage was again

begun, but the growth increased in size in spite of intensive doses given over the right and left anterior and posterior lower abdominal quadrants. On August 28 the patient died.

Autopsy.—The body of this patient was well developed but poorly nourished. A bulging tumor was present beneath a partly healed midabdominal surgical incision. Its entire central portion was soft and necrotic and formed a cavity, in which a rubber drain was found. This tumor was extremely hard and was intimately connected with the overlying skin and the scar. It appeared to penetrate deeply into the abdominal cavity and also into the skin and subcutaneous

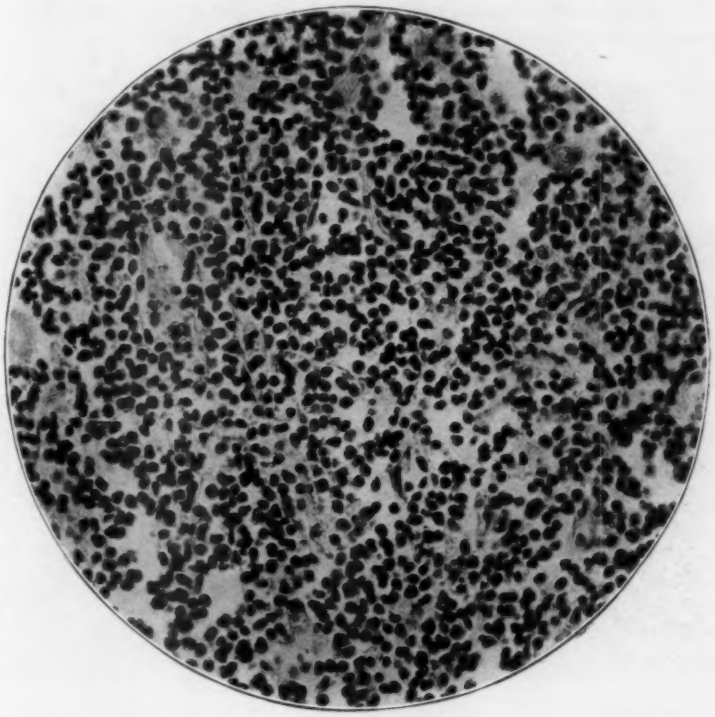

Fig. 3.—Low power view of tumor tissue from prostate gland.

tissues over the symphysis pubis. Several hard inguinal lymph nodes were felt on palpation.

When the peritoneal cavity was opened, an extremely large tumor was found occupying the entire pelvis. This mass extended to about 5 cm. above the umbilicus. The omentum, very poor in fat, was drawn upward, leaving the intestinal loops uncovered. The liver edge extended about 6 cm. below the costal margin. The serosa of the intestinal loops was covered by a fibrinous exudate, which glued adjacent coils lightly together. There was a small amount of a purulent exudate in the dependent part of the cavity. The mesentery was studded with small and large metastatic nodules. Along the entire course of the abdominal portion of the aorta were large, hard lymph nodes, many of them matted together.

The pelvic tumor mass with the overlying skin and scar and all organs attached to or buried within it was carefully mobilized and taken out en bloc. This mass measured 22 cm. in length, 17 cm. in width and about 17 cm. in thickness (fig. 1). On section the cut surfaces were yellowish white and very hard. In the center, however, and in places extending to the surface, the mass was discolored and showed extensive necrosis and softening. No evidence of prostatic tissue could be found, which may be explained on the basis of the previous prostatectomy. The bladder, which overlay the growth, appeared necrotic, and its mucosa was covered by a dirty, dark grayish brown material, which could be scraped off easily with a knife. Extending from the outer wound into the bladder cavity there was an inflamed sinus tract, which measured about 1.5 cm. in width. The old scar and the wound were diffusely infiltrated by tumor tissue, and sections through the

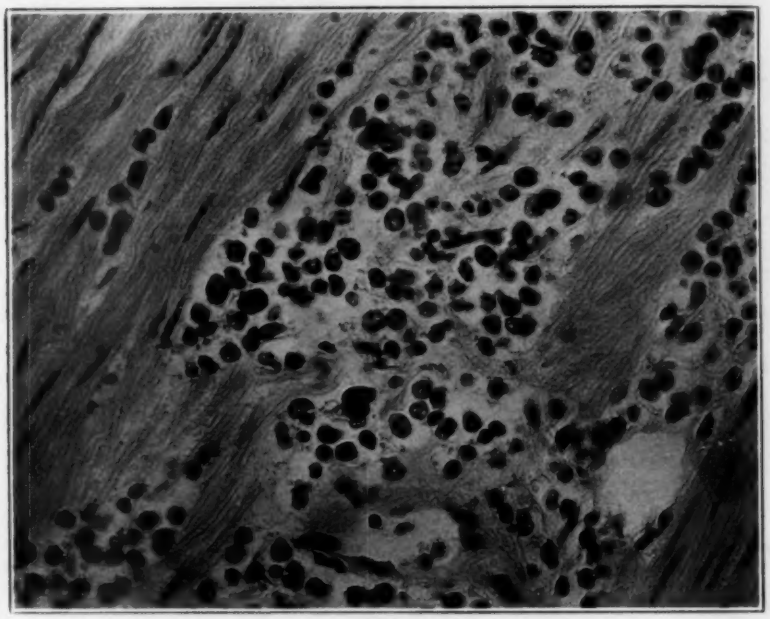

Fig. 4.—High power view of tumor tissue infiltrating the rectus abdominis muscle. Note the occasional appearance of multinucleated tumor cells.

deferent ducts and the ureters showed these structures to be completely embedded in neoplastic tissue. The new growth also had invaded the symphysis pubis.

Except for the incarceration within the pelvic tumor of the sigmoid colon and retrocecally situated appendix, the gastrointestinal tract did not disclose any tumor involvement.

The lungs, except for several circumscribed tumor nodules near the pleurae, were not unusual.

The pancreas weighed 115 Gm. and was rather hard to palpation. It cut with increased resistance and was surrounded by several large, hard nodules of grayish white appearance, apparently lymph nodes, infiltrated by metastases. The adrenal glands were not remarkable except for the fact that they were surrounded by firm tumor tissue.

The kidneys were surrounded by thick, hard, nodular capsules, which on section were grayish white and neoplastic. The right kidney weighed 185 Gm.; the left, 250 Gm. When the thickened capsules were removed, numerous small cortical abscesses filled with creamy pus projected from the surface of each organ. Grossly it could not be determined definitely whether or not any tumor metastases were present. The pelves were markedly dilated and contained a thick purulent exudate. Their mucous surfaces were markedly congested and inflamed. Both ureters were dilated and their lumens filled with pus. In some places their walls averaged 0.1 cm. in thickness. Their inferior portions disappeared in the tumor mass. On the right side the hypogastric artery entered the tumor mass and was lost completely for part of its course. It emerged again about 1 cm. above the inguinal canal. On the left side tumor tissue lay close to, but

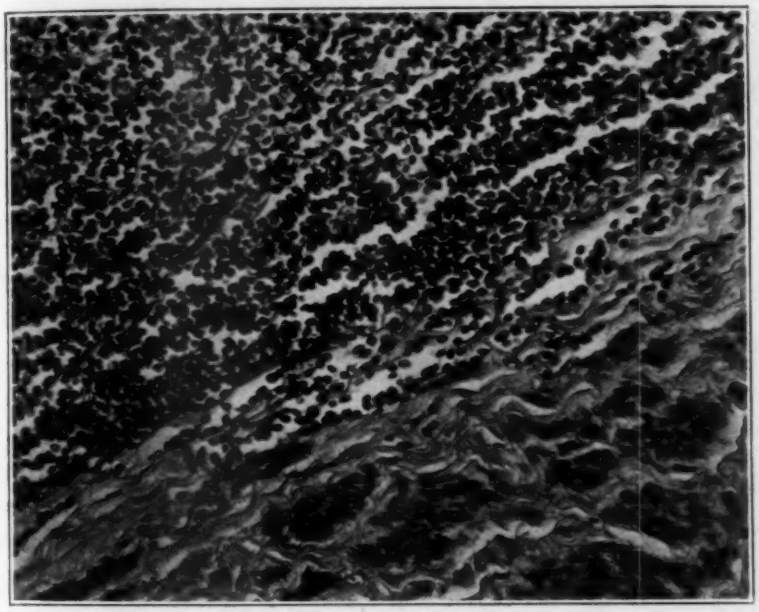

Fig. 5.—Low power view of tumor tissue infiltrating the adventitia of the right hypogastric artery.

did not surround or invade, the hypogastric artery. Both deferent ducts were embedded in neoplastic tissue, but they also emerged again from the tumor to enter in normal fashion into the scrotal sac. The skin above and directly below the symphysis pubis contained several metastatic nodules. None were seen in the skin of the scrotum or the penis.

Microscopic Examination.—Sections from different viable portions of the large pelvic tumor showed it to be histologically a homogeneous new growth composed of small, irregularly rounded, undifferentiated cells which formed no structure, assumed no characteristic arrangements and appeared as discrete entities. In general the cells resembled lymphocytes or cells of the lymphocytic series (fig. 3). The type cell was small, irregularly round or oval, with a minute amount of faintly staining, slightly acidophilic cytoplasm and a round or ovoid nucleus, which

was almost as large as the cell itself. The nucleus tended to be hyperchromatic with a distinct nuclear membrane and contained a moderate amount of deeply staining, finely granular chromatin. While the majority of the neoplastic cells were small, measuring from 6 to 8 microns in diameter, moderate numbers of them were quite large, some being 12 microns wide. Occasionally multinucleate giant cells were found (fig. 4). Many of the cells were actively growing, as indicated by the presence of mitotic figures in all phases. The neoplasm infiltrated all tissues widely. In the rectum the serosal surface was extensively infiltrated, and in some sections the new growth penetrated the two smooth muscle layers and invaded the submucosa and even the mucosa. In the sigmoid colon, neoplastic invasion of the serosa and muscularis was marked, but the submucosa and mucosa were not involved. The periappendical fat was likewise infiltrated, and in some

Fig. 6.—Silver preparation of tumor tissue, showing the abundant fine reticulum.

situations even the muscularis was invaded. The adventitia of the hypogastric arteries, particularly that of the right, was diffusely infiltrated (figs. 2 and 5), and the walls of the ureters and the deferent ducts showed invasion which in some situations extended as deep as the epithelial linings of their lumens. Even in the anterior abdominal wall there was extensive infiltration of all tissues from subperitoneal fat through the strands of the rectus muscle into the skin and subcutaneous tissue. In the latter situation the neoplastic cells resembled lymphocytes much more definitely than did the tumor cells in the pelvic mass (fig. 4).

In many situations the neoplastic tissue showed degenerative changes which varied from pyknosis and karyorrhexis with granular or hyaline degeneration of the cytoplasm to necrosis and the disappearance of great numbers of tumor cells, with resulting softening and liquefaction of the growth. It is probable that these changes were due, in part at least, to intensive irradiation.

Sections from the bladder wall showed extensive infiltration of the muscle up to the edematous, chronically inflamed mucous membrane. In the specimens examined the mucosa was not involved, however.

Where the neoplasm invaded fat tissue, large vacuolated cells with vesicular nuclei were often mixed with the tumor cells. Sometimes these cells also contained dark-staining granular nuclear material. They were interpreted as macrophages containing fat and granular material from disintegrated tissue. In some situations lymph channels and possibly even small blood vessels were found to contain typical tumor cells.

A section of a part of the new growth which infiltrated fat was stained by the method of Foot and Foot for the demonstration of reticulin fibrils. Throughout the entire metastatic growth delicate reticulin fibrils were present between the tumor cells. They were considered to have been formed by the tumor cells (fig. 6). Sections from many of the metastases were also examined. In all situations, notably in the pancreas, in the perirenal and periadrenal fat and in the lungs and pleurae, the histologic and cytologic characters of the growth were similar to those already described, except for the fact that, if anything, the tumor cells even more closely resembled lymphocytes and lymphoblasts than did the cells of the primary tumor. The final pathologic diagnosis was: lymphosarcoma, reticulum cell type, of the prostate gland with extensive invasion of the surrounding tissues and widespread generalized metastases to aortic abdominal, peripancreatic and mesenteric lymph nodes, lungs and pancreas.

COMMENT

Evaluation of the reported cases of lymphosarcoma of the prostate gland is difficult, since no definite and accepted criteria for the classification of the various prostatic malignant tumors have been established. Attempts at classification have been made by various investigators (Proust and Vian [11]; Smith and Torgerson [12]; Randall and Boland [13]; Costa [14]; Lowsley and Kimball [15]) but unanimity of opinion is far from complete even in these careful critiques. It is particularly in the cases of sarcoma, small round cell sarcoma, lymphosarcoma and anaplastic carcinoma of the prostate gland that classification appears to be most difficult. We do not wish at this time to discuss prostatic tumors in general but rather to consider only the lymphosarcoma in the light of the observations made by others as well as by ourselves.

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11. Proust, R., and Vian, E.: Le sarcome de la prostate, Ann. d. mal. d. org. génito-urin. **25**:721-778, 1907.

12. Smith, R. R., and Torgerson, W. R.: Sarcoma of the Prostate, Surg., Gynec. & Obst. **43**:328-337, 1926.

13. Randall, A., and Boland, H.: A Critique of Prostatic Sarcoma, Tr. Am. A. Genito-Urin. Surgeons **22**:245-260, 1929.

14. Costa, A.: Malignità e transformazione maligna del mioma (leiomioma maligno della prostata), Tumori **14**:115-142, 1928.

15. Lowsley, O. S., and Kimball, F. N.: Sarcoma of the Prostate, with a Review of the Literature, Brit. J. Urol. **6**:328-348, 1934.

In the opinion of Ewing,[16] even the possibility of lymphosarcoma ever occurring in the prostate gland should be seriously questioned. He argued that the architecture of this gland does not favor the development of lymphosarcoma. This view, however, appeared too skeptical to Wegelin, and Symmers pointed out that the prostate gland belongs to the so-called auxiliary lymphoid systems, with the adrenal glands, lungs, liver, kidneys, testes and other organs. He expressed the belief that the gland normally contains interstitial lymphoid foci, which under ordinary circumstances are likely to be overlooked but which in certain cases of disease may be readily identified. He concludes that there is no apparent reason why a tumor of lymphoid cells should not spring from such a focus in the prostate. In a recent personal interview with one of us, Dr. Ewing admitted the possibility of a lymphatic tumor in the prostatic gland.

Thus even the possibility of primary prostatic lymphosarcoma is controversial. Actual studies of prostate glands to demonstrate the presence of lymphoid tissue occurring normally or to trace its development in disease of the organ are rare. Most of those which have been made were carried out on experimental animals, particularly dogs. In 1900 Walker[17] found lymphoid tissue in human and animal prostate glands. Shortly thereafter Weski[18] reported a study of an island of lymphoid tissue in a dog's prostate, an occurrence previously noted by Waldeyer. He regarded this finding as pathologic, although no other evidence of any disease could be found in the animal. Later he demonstrated lymph nodules in 2 human prostate glands and pointed out that they were normal structures. Similar observations were made by Deaver[19] and by Wilson and McGrath.[20] More recently Fukase[21] studied 222 prostates obtained at operations and autopsies and found that small, primitive or rudimentary lymph nodes occur normally throughout the gland in the form of small aggregations of lymphocytes, located beneath the glandular and duct epithelium, particularly toward

16. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 852.

17. Walker, G.: A Contribution to the Study of the Anatomy and Physiology of the Prostate Gland, and a Few Observations on the Phenomenon of Ejaculation, Bull. Johns Hopkins Hosp. **11**:242-256, 1900.

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21. Fukase, N.: Hyperplasia of the Rudimentary Lymph Nodes of the Prostate, Surg., Gynec. & Obst. **35**:131-136, 1922.

the outlets of the ducts. He considered them to be analogous to the rudimentary lymph nodes found in other organs, such as the liver, kidneys and uterus.

Fukase also went so far as to differentiate between normal rudimentary lymph nodes, hyperplastic nodes and inflammatory infiltration. The normal rudimentary lymph nodes were found in all normal adult human prostate glands and consisted of small aggregations of small lymphocytes, slightly more crowded at the periphery than at the center, but not possessing any well defined germinal centers. They could not be seen with the naked eye in stained sections. The hyperplastic nodes varied in size from 0.15 mm. to 0.5 mm. or larger, so that they could be seen with the naked eye in stained preparations. Well defined germinal centers were found in the largest ones. The inflammatory infiltrations were "readily" distinguished from the rudimentary lymph nodes by the uniform character of the cells, the arrangement of these cells, the demonstration of the endothelium of the lymphatic vessels and the fibrils of the reticulum.

It was Fukase's belief that hyperplasia of these rudimentary lymph nodes of the prostate gland occurred chiefly in chronic hyperplastic prostatitis and carcinoma.

Also Wegelin felt that while lymphatic tissue is probably normally not present in the prostate gland, as a result of chronic inflammation with destruction of muscle tissue and overgrowth of connective tissue accompanying hypertrophy, true lymph follicles with germinal centers may definitely develop.

In our own experience lymphoid tissue with and without germinal centers is frequently seen in prostate glands. In the absence of any systematic study of this controversial subject on our part we are not qualified to substantiate Fukase's and Wegelin's observations. However, the foregoing observations led to the suggestion by Ferguson and Stewart that lymphosarcoma may originate from lymphoid tissue which arises as a result of old past inflammation of the genitourinary tract, such as gonorrhea, a supposition also adopted by Rathbun and deVeer. In our patient's case, no such history of past inflammation could be elicited, so that here the question must remain unanswered.

The question as to whether or not these tumors, including our own, are really lymphosarcoma and not highly anaplastic carcinoma—the most frequent type of malignant neoplasm of the prostate gland—must perforce be raised. In part this has already been discussed. Although we feel that Quinby's case, for example, can be accepted as one of primary prostatic lymphosarcoma, Randall and Boland pointed out that the tumor presented a number of features "not so infrequently seen" in prostatic carcinoma. Indeed in our own case a diagnosis of anaplastic

carcinoma was made by one of us (A. W. W.) on the second biopsy. Sections of this tissue showed atypical, anaplastic cells which tended at times to grow in groups or masses much as undifferentiated cells of carcinoma would. It must be borne in mind, however, that this biopsy included only a minute portion of a large tumor, which in different parts presumably showed different features. The multiple tumor sections examined post mortem, however, leave no doubt that we are dealing here with lymphosarcoma, not carcinoma. It is also noteworthy that there were no bone or lung metastases, so characteristic of primary prostatic carcinoma. In this case the spread appeared to be purely lymphatic or by direct extension.

Although we do not wish to emphasize too strongly the presence of multiple and readily visible reticulum fibrils, seen in silver preparations, as supporting the diagnosis of lymphosarcoma, we feel that their presence at least speaks against a diagnosis of carcinoma.

Whether, finally, the new growth originated really in the prostate gland and not in the urinary bladder, from which it invaded the prostate gland secondarily, is a matter of conjecture. Since both organs were widely involved and the prostate itself was actually unrecognizable at the time of autopsy, it would appear difficult to state with certainty from postmortem study alone that the growth originated in the prostate gland. However, from the clinical investigations in this case we feel sure that the tumor originated in that organ. Also from the frequent observations of lymphatic tissue in prostate glands examined in this laboratory we feel that the possibility of the development of lymphosarcoma is not remote.

Of great interest in this patient was the fact that the tumor proved to be extremely radioresistant, even growing rapidly larger during and after intensive treatment with roentgen rays of high voltage. This of course is not a definite point of differentiation between lymphosarcoma and anaplastic carcinoma, particularly since lymphosarcoma in general is quite radiosensitive and this growth was certainly not. Nevertheless the present case as far as we can determine is the fourth one in which prostatic lymphosarcoma received extensive high voltage roentgen irradiation without benefit.

SUMMARY

Lymphosarcoma of the prostate gland is a rapidly growing neoplasm which infiltrates the surrounding tissues diffusely, produces widespread metastases and proves fatal in from three to nine months. It may occur in any age period but appears more frequently in early adult life. Its causes are somewhat obscure, but it may arise from the preexisting lymphatic tissue in the gland or from the hyperplastic lymphoid tissue formed as a result of chronic inflammation (compare sarcoma in Hodg-

kin's disease). Radiation therapy appears to be without any beneficial effect in the treatment of lymphosarcoma of the prostate gland; in fact, it may enhance the growth of the tumor. In establishing the diagnosis of lymphosarcoma of the prostate gland extreme care must be taken to scrutinize all clincial, therapeutic, gross anatomic and histologic charasteristics of the new growth in order to avoid confusion with highly anaplastic carcinoma, the most frequent type of malignant tumor of this organ.

Dr. John E. Heslin gave us permission to make use of the clinical data in the case reported.

ANTERIOR RESECTION FOR CANCER OF THE RECTOSIGMOID

J. E. DUNPHY, M.D.
BOSTON

It is well established that abdominoperineal resection in one or more stages is the operation of choice for cancer of the rectum. Less extensive procedures are justifiable only when the radical operation is specifically contraindicated. However, when one is dealing with cancer of the rectosigmoid, the situation is less clear, for it is possible that in selected cases anterior resection of the rectum followed either by anastomosis or by closure of the rectal stump with permanent colostomy may prove equally satisfactory. Anterior resection offers hope of avoiding permanent colostomy and since it is a less extensive procedure, should have a lower operative mortality.

The rectosigmoid is that portion of the large intestine in which the narrow sigmoid colon undergoes a gradual enlargement before joining the rectum. Its exact position is variable. By some it has been estimated to be about 2 inches (5 cm.) above the superior valve of Houston. Others place it as lying opposite the third sacral vertebra. For the purpose of this discussion it may be described as that portion of the pelvic colon in which a neoplasm cannot be delivered sufficiently high to permit a satisfactory end to end anastomosis or Mikulicz resection and yet is not in the ampulla of the rectum. The frequency of malignant lesions in this area is not inconsiderable. Pemberton and Dixon [1] found that 17 per cent of over 3,000 cancers of the colon and the rectum were in the rectosigmoid. Of the 270 patients with cancer of the colon and the rectum admitted to the Peter Bent Brigham Hospital during the five year period covered by this study (1934 to 1939), 24 had the lesion in the rectosigmoid.

There are several anatomic and pathologic factors which make neoplasms in this area worthy of especial consideration. At this point the mesosigmoid becomes shortened, and just below this area it disappears entirely, leaving the bowel with a peritoneal covering on the anterior side only. The blood supply comes from the terminal branches of the

From the Surgical Clinic of the Peter Bent Brigham Hospital.

1. Pemberton, J. de J., and Dixon, C. F.: Summary of End-Results of Treatment of Malignancy of Thyroid Gland and Colon, Including Rectum and Anus, Surg., Gynec. & Obst. **58**:462 (Feb., no. 2A) 1934.

superior hemorrhoidal artery, and an adequate resection of the possible areas of lymphatic extension necessitates destroying this vessel. Thus the vascular supply to the resected ends of the bowel must be supplied by the variable and inconstant middle hemorrhoidal arteries and the marginal branch of the sigmoidal arteries. Finally, there is the possibility that cancer of the rectosigmoid may extend to the lymphatics below the point of resection, that is, to the tissues about the rectum proper. For these various reasons many surgeons feel that an abdominoperineal resection is the operation of choice for lesions in this area.[2] In recent years, however, there has been a revival of interest in segmental resection of the pelvic colon.[3] In general, the reports of the surgeons using this type of resection have been favorable. In this paper the more recent experiences at the Peter Bent Brigham Hospital are recorded.

ANALYSIS OF CASES

During the period 1934 to 1938, inclusive, 24 patients with cancer of the rectosigmoid were cared for in the Peter Bent Brigham Hospital. In 3 instances no operation was performed because of evident extensive metastases. In 6 cases an exploratory laparotomy followed by colostomy was done. There were 2 postoperative deaths. None of the patients survived more than one year after operation. In 15 cases the lesion was considered operable; 7 of the patients were treated by abdominoperineal resection, and 8 were treated by anterior resection, followed in 2 instances by an immediate end to end anastomosis. The operative mortality, survival periods and pathologic gradings in these 15 cases are detailed in the table. The series is too small to permit of statistical evaluation, but several observations are worthy of note. There were 2 deaths in the group of patients operated on by abdominoperineal resection. There were no deaths among the patients on whom anterior resection was performed. Four of the 5 patients operated on by the abdominoperineal route were alive and well without evident recurrence at the time of the last follow-up visit; 6 of the 8 patients surviving anterior resection were well without recurrence at the time of writing. There is a close correlation between the pathologic grading of the lesions and recurrence. To date there has been no recurrence among those patients graded A or B. It is unfortunate that in both the patients on whom anastomosis was performed, the lesion was extensive.

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2. Rankin, F. W., and Graham, A. S.: Cancer of the Colon and Rectum, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

3. Horsley, J. S.: Resection of the Rectosigmoid and Upper Rectum for Cancer, with End-to-End Union, Surg., Gynec. & Obst. **64**:313 (Feb., no. 2A) 1937. Dixon, C. F.: Surgical Removal of Lesions Occurring in the Sigmoid and Rectosigmoid, Am. J. Surg. **46**:12 (Oct.) 1939.

Two of the cases in which anterior resection was performed (cases 9 and 10) will be discussed in more detail because they illustrate a particular application of this type of operation which has not been given due consideration.

CASE 9.—The patient was a 39 year old woman who first entered the Peter Bent Brigham Hospital in the summer of 1936 with acute obstruction of the large bowel due to a malignant growth in the sigmoid. A preliminary colostomy was done followed by a resection of the tumor with an end to end anastomosis; after this the colostomy opening was closed. The growth was adenocarcinoma, growing fairly rapidly, with numerous lymph node metastases. The patient was well for the next eighteen months. At the end of that time, however, she reentered the hospital because of profuse bleeding from the rectum. Examination showed her

Operative Mortality, Survival Periods and Pathologic Gradings in Fifteen Cases of Cancer of the Rectosigmoid

Case	Operation	Operative Death	Survival Period at Time of Last Follow-Up	Pathologic Grading *
1	Abdominoperineal resection	0	1.2 years; dead	C3
2	Abdominoperineal resection	0	3 years	A2
3	Abdominoperineal resection	0	5 years	A2
4	Abdominoperineal resection	+	0	A2
5	Abdominoperineal resection	+	0	B2
6	Abdominoperineal resection	0	2 years	A2
7	Abdominoperineal resection	0	3 years	B2
8	Anterior resection	0	2 years	B2
9	Anterior resection	0	4 years	C2
10	Two stage anterior resection †	0	2 years	B2
11	Anterior resection with anastomosis	0	6 months; dead	C3
12	Anterior resection	0	2 years	B2
13	Anterior resection	0	8 months; dead	C3
14	Anterior resection	0	2 years	A1
15	Anterior resection	0	1 year	B2

* The method of classification is essentially that of C. E. Dukes (Classification of Cancer of the Rectum, J. Path. & Bact. **35**: 323 [May] 1932). Grade A indicates that the lesion is confined to the bowel wall; grade B means local extension; grade C indicates metastasis to lymph nodes. The figures 1, 2 and 3 refer to the rate of growth of the tumor as estimated microscopically: 1 indicates slow growth; 2, intermediate growth; 3, rapid growth.

† See text for details.

to be in good general health, but a large fixed mass was palpable in the left lower quadrant of the abdomen. By a roentgen examination after she had been given a barium sulfate enema and sigmoidoscopy together with biopsy adenocarcinoma was demonstrated at the site of the previous resection. Here, then, was a young woman with an early recurrence of a rapidly growing sigmoid neoplasm with proved metastasis to lymph nodes. Was an exploratory operation justifiable? It is my feeling that unless distant metastases can be demonstrated, a patient with recurrent neoplasm of the colon should be submitted to an exploratory procedure even though clinically the growth seems of doubtful operability.

A second operation was performed and an extensive tumor mass observed just below the brim of the pelvis. It was adherent to the lateral parietes, the left adnexa and the broad ligament. Extensive resection was performed, and the remainder of the sigmoid and the pelvic colon down to the upper part of the rectum were removed. The left ovary and the broad ligament were included in the resection. The rectal stump was inverted but left above the pelvic floor. Except

for an iliac abscess which required drainage, the postoperative course was uneventful. This patient was alive and well, without evidence of recurrence at the time of writing, four years after the operation.

In this instance an anterior resection was performed to extend the scope of resection of a tumor of the lower part of the sigmoid. A less extensive operation with another anastomosis above the pelvis might have been performed, but in view of the initial recurrence of the growth it was thought that radical resection with the acceptance of a colostomy was the preferable procedure. The use of anterior resection under such circumstances has not been given due consideration. The possibility of

Fig. 1.—Roentgenogram showing two constricting lesions of the colon, one in the descending portion and the other in the lower part of the sigmoid.

avoiding colostomy in this type of resection by an anastomosis in the hollow of the sacrum will be discussed later.

Case 10.—A 54 year old woman entered the hospital because of fever, chills and pain in the left lower part of the abdomen. Physical examination disclosed a large, easily palpable, acutely tender mass in the left lower quadrant of the abdomen and the left vault of the vagina. Roentgen examination after the administration of a barium sulfate enema showed two rather extensive areas of narrowing of the large bowel, one in the lower part of the sigmoid and one in the midportion of the descending colon (fig. 1). After a period of ten days of preparation, during which the white blood cell count and the temperature became normal and the

pelvic mass decreased in size, operation was performed. There were two separate neoplasms, one in the descending colon—a long constricting lesion without evident local extension or metastases—and a larger rounded lesion, about 15 cm. in diameter, in the lower part of the sigmoid. The latter lesion was adherent to several loops of small bowel, to the bladder and to the left lateral wall of the abdomen. Although there were considerable edema and inflammation in the lower lesion, operability appeared doubtful. However, without distant metastases the operability of sigmoidal or rectal lesions is exceedingly difficult to evaluate in the presence of any degree of inflammation. Diversion of the fecal stream must be done and a reevaluation of the tumor made after a period of ten days to three weeks. Accordingly, the splenic flexure was demounted and the proximal lesion resected. The transverse colon was then brought through the upper portion of the left rectus incision as a permanent colostomy, and the lower loop of the bowel was brought through the opposite end of the wound as a distal colostomy. The omentum was attached along the mesentery of the lower loop of the bowel in an effort to exclude this area as much as possible from the rest of the abdomen.

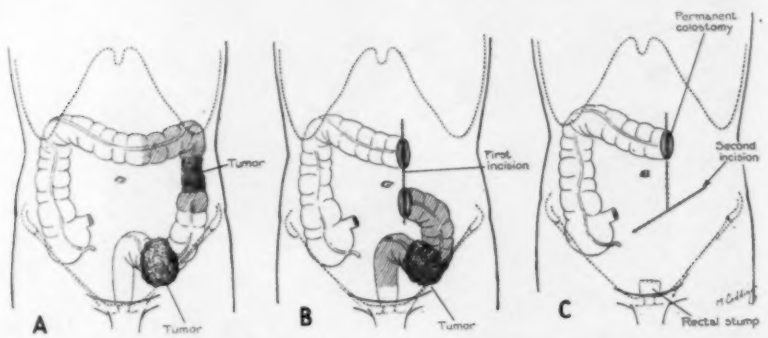

Fig. 2.—A plan used for resection of dual carcinoma of the colon when the distal growth is an extensive one of doubtful operability. A period of three weeks elapsed between the two stages.

The plan of resection is shown in figure 2. It constitutes an application of the principle of the Lahey two stage resection [4] to a low sigmoidal growth of doubtful operability. Ordinarily it would not be used except for a lesion in the rectum, but the presence of a dual lesion, one of which was of borderline operability, made it desirable. After operation the distal colon was irrigated daily, and at the end of three weeks the second operation was performed. This was done through an oblique incision in the lower part of the abdomen; the incision included the lower end of the first incision (fig. 2). There was an amazing regression of the size of the tumor mass. It was now possible to free it from the small bowel. The apparent extension to the bladder and abdominal wall was confined to the peritoneal surfaces so that the entire lesion was easily removable. This was accomplished again by means of an anterior resection, by which the superior hemorrhoidal vessels were destroyed and all the pelvic colon was removed. The rectal stump was closed but again left intraperitoneally. Convalescence was uneventful. This

4. Lahey, F. H., and Cattell, R. B.: Two-Stage Abdominoperineal Resection of the Rectum and Rectosigmoid for Carcinoma, Am. J. Surg. **27**:201 (Feb.) 1935.

patient was alive and well at the time of writing, two years since operation. This, again, represents the adoption of anterior resection to permit of a more radical attack on an extensive lesion of the lower part of the sigmoid. I believe that the use of a two stage procedure in this manner permitted the resection of a sigmoidal growth which might otherwise have been considered, and, if attempted in one stage, might have proved inoperable.

AVOIDANCE OF COLOSTOMY

To advocate anterior resection as a means of avoiding colostomy in cases of cancer of the upper part of the rectum is dangerous. Recurrent cancer is too high a price to pay for avoiding colostomy. On the other hand, there are a considerable number of cases of cancer of the rectosigmoid or the lower part of the sigmoid in which an adequate resection must include the superior hemorrhoidal vessels but in which an abdominoperineal resection is not necessary. The comparative areas removed

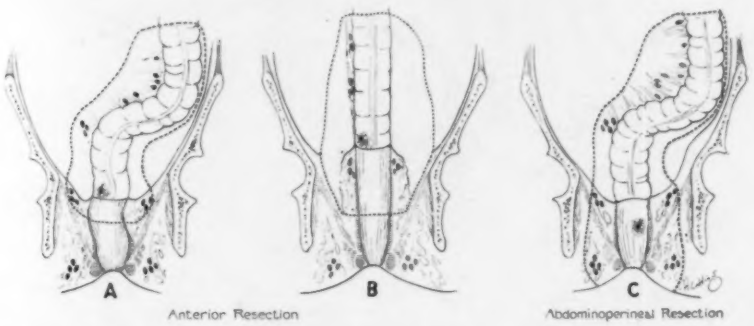

Fig. 3.—The comparative extent of the resections accomplished by the anterior (*A* and *B*) and the combined abdominoperineal resection (*C*). Anterior resection should be employed for a tumor of the rectosigmoid only when an adequate margin can be developed below the tumor by freeing the rectum from the hollow of the sacrum (*B*).

by anterior resection and abdominoperineal resection are shown in figure 3. It can be seen that if the lesion is sufficiently high, enough room is gained by freeing the rectum from the hollow of the sacrum to permit fully as extensive a resection as is accomplished when a low-lying rectal lesion is removed by the combined route. Only when there is room for adequate resection by the anterior route should the operation be utilized, and it is only under these circumstances that avoidance of permanent colostomy can justifiably be permitted. The precise indications for anterior resection as opposed to abdominoperineal resection await clarification on the basis of careful pathologic study of resected specimens and follow-up data gathered over a long period.

TECHNIC OF ANTERIOR RESECTION

There are three indications for preliminary colostomy, namely, intestinal obstruction, a large growth of borderline operability and contemplated immediate end to end anastomosis. Sometimes colostomy is done as a preliminary procedure; at other times the region of the growth is first explored and then, if necessary, colostomy is performed. When anterior resection with closure of the rectal stump is contemplated, preliminary colostomy is rarely indicated.

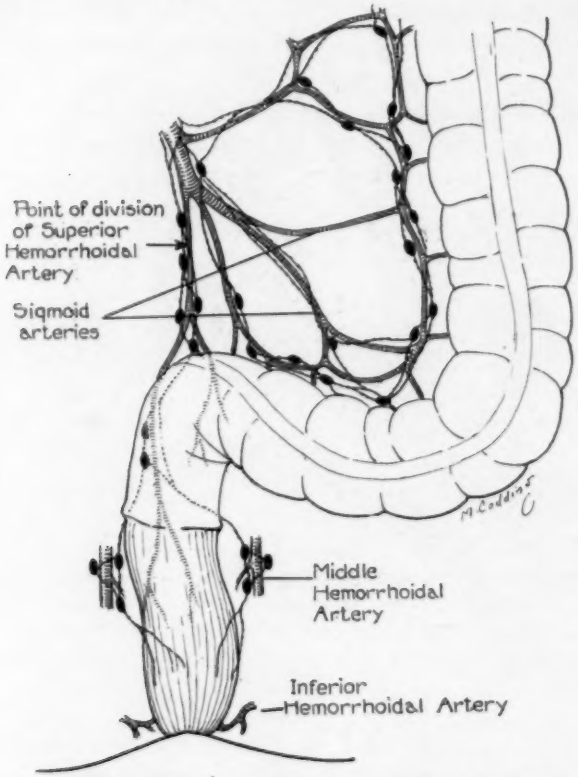

Fig. 4.—Point of ligation of the superior hemorrhoidal artery in anterior resection. If anastomosis is contemplated, great care must be taken to preserve the lower part of the sigmoid and the marginal branch of the sigmoid arteries.

Colostomy is best done on the right side of the transverse colon; this permits mobilization of the splenic flexure in the event that there is an unusually short sigmoid loop. In my experience transverse colostomy of the permanent type, as advocated by Cheever,[5] has proved the most satisfactory means of preparing the distal colon for resection. It is

5. Cheever, D.: The Choice of Operation in Carcinoma of the Colon, Ann. Surg. **94**:705 (Oct.) 1931.

superior to cecostomy because it completely diverts the fecal stream. Compared with a Devine colostomy [6] it is a less serious operation for the patient and is easier to make and much easier to close for the surgeon, and we believe it provides for fully as satisfactory cleansing of the distal colon.

Resection is performed ten days to three weeks after colostomy. The abdomen is opened through a left paramedian incision, the rectus muscle being laterally retracted. After determination of the extent and the operability of the growth (unless this has been done at the time of

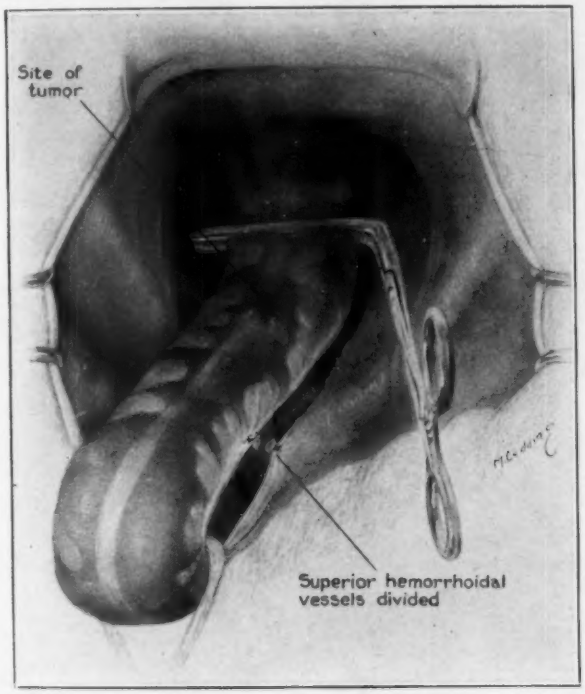

Fig. 5.—Anterior resection of the rectum. The ureters have been identified; the superior hemorrhoidal artery has been divided, and the pelvic colon freed down to the suspensory ligaments of the rectum. A right-angled clamp is placed across the bowel well below the tumor.

colostomy), the peritoneal reflections of the pelvic mesosigmoid are opened from just above the promontory to the hollow of the sacrum. The pelvic colon is mobilized and the ureters identified. The superior hemorrhoidal artery is then divided below the last sigmoidal branch (fig. 4). The peritoneum is then opened anteriorly between the bladder or the uterus and the rectum, and the entire bowel is freed, care being

6. Devine, H.: Excision of Rectum, Brit. J. Surg. **25**:351 (Oct.) 1937.

taken not to injure the region of the middle hemorrhoidal vessels. If by these maneuvers a generous margin has been developed below the tumor, anterior resection is done. The upper part of the sigmoid is divided between clamps, and then a right-angled clamp is placed across the lower segment (fig. 5). As the bowel is divided below this point, the rectum is secured with Allis forceps (fig. 6). There is little or no danger of spilling or leakage from the lower segment, but this maneuver assures a clean field while the bowel is being divided and yet does not compromise the blood supply of the lower segment by crushing it in a

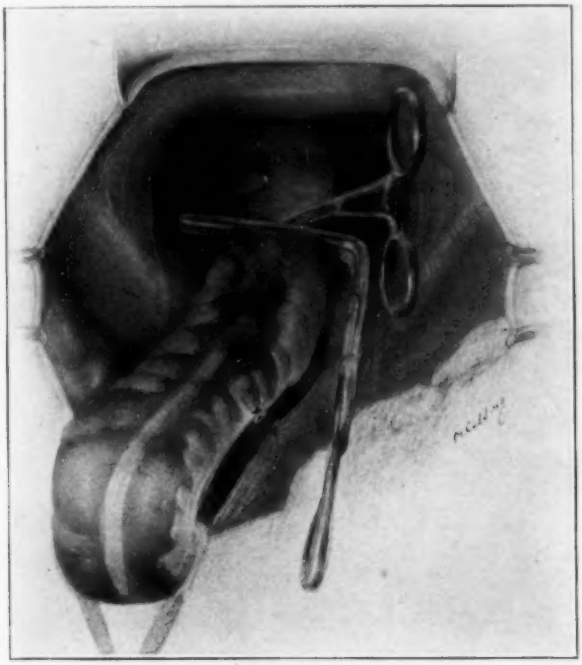

Fig. 6.—Anterior resection of the rectum. A distal clamp is not used. As the bowel is divided with the cautery, the stump of the rectum is secured with Allis forceps.

clamp. After removal of the tumor the lower segment is closed by a continuous inverting suture of fine catgut on an atraumatic needle, reenforced with serosal sutures of fine silk. If anastomosis is planned, the procedure is as follows: By gentle traction on the Allis forceps the lower segment is elevated while the upper segment is brought down to it, and the posterior layer of serosal sutures is placed and tied (fig. 7 *A*). The Allis forceps are then removed; the bowel is opened, and the anastomosis is completed (fig. 7 *B, C*). A curved spring-bladed enterostomy clamp is kept on the upper segment during anastomosis (fig. 7). I

believe that an open anastomosis is preferable to a closed anastomosis in this situation because it permits one to be certain of an adequate blood supply to the resected ends of the bowel and because it assures accurate placing of sutures, assuring a water-tight anastomosis.[7] After completion of the anastomosis the peritoneal floor is closed. In the 2 cases included in this study the anastomosis was left below the reconstructed pelvic floor. It is advisable to drain the retroperitoneal space whenever the line of resection is left below the peritoneal floor. The colostomy is closed ten days to three weeks after the resection. This is a comparatively minor procedure, readily done with the area under local anesthesia.

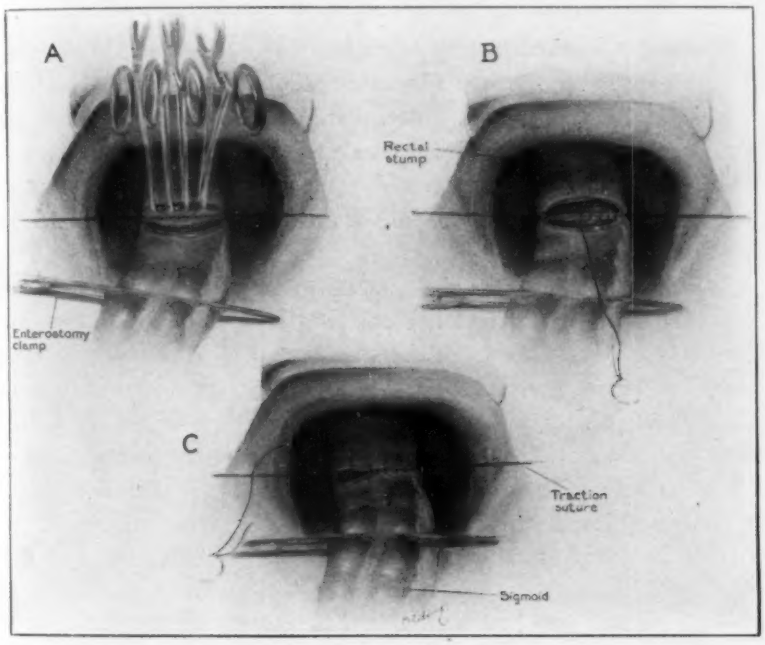

Fig. 7.—Anterior resection of the rectum. After division of the bowel, the distal stump is closed with a continuous inverting suture of catgut, reenforced with serosal sutures of silk; or, in exceptional cases, anastomosis is performed as shown.

SUMMARY

Recent experiences with anterior resection in the management of cancer of the rectosigmoid are recorded. Emphasis is placed on the use of this procedure to extend the scope of resection in cases of lesions of the lower part of the sigmoid rather than to limit the areas of resection in cases of cancer of the upper part of the rectum. A technic of resection which has proved satisfactory is outlined.

7. Cutler, E. C., and Zollinger, R.: Atlas of Surgical Operations, New York, The Macmillan Company, 1939.

SURGICAL ASPECTS OF PAIN IN THE ABDOMEN IN RELATION TO CLAIMS FOR COMPENSATION

LOUIS RENÉ KAUFMAN, M.D.
NEW YORK

If the physician is to evaluate the symptom of abdominal pain as a basis for compensation, he should be alert in determining its significance by obtaining a detailed history and carrying out a careful examination supplemented by appropriate laboratory study. For pain is a universal symptom, and if it is preponderant, there may be difficulty in establishing its significance with respect to a claim for compensation. The pain must be proved to be the result of a compensable cause.

In relation to compensation, pain in the abdomen may be divided into three categories:

First there is pain in the abdomen resulting from the specific hazards of an occupation, as for instance painter's colic or the pain associated with hematuria resulting from the specific tumor of the bladder which occurs in aniline dye workers. The history and the physical examination will establish pain of this type as clearly the result of an occupational hazard and, as such, it reasonably entitles the patient to compensation.

The second type of pain in the abdomen is that produced by trauma in a patient otherwise free from disease. Such trauma includes not only injury by a sharp or a blunt object but likewise that resulting from muscular contraction, as in the strain of lifting, or from a fall. The first evidence of abdominal trauma is pain, but its intensity, distribution and persistence will vary according to the effect of the trauma on the walls or on the viscera and other structures of the abdomen.

In the third category is pain which is the effect of occupation and especially of occupational trauma on a preexisting lesion in the abdomen. This group demands careful determination of the many factors involved. What would have been the natural course of the disease, for example, is an important question in evaluating the effect of a fall in precipitating gastric hemorrhage in a patient with peptic ulcer.

Presented at the meeting of the Association for the Advancement of Industrial Medicine and Surgery, May 1941.

From the departments of surgery of the Flower and Fifth Avenue Hospitals and the Metropolitan Hospital.

The need of establishing exactly the relation of trauma to an abdominal lesion is emphasized by the following case in which much confusion resulted from a clear history of previous injury.

CASE 1.—H. P., a 28 year old elevator operator, was admitted on Aug. 10, 1937 and discharged on September 25. His chief complaint was pain in the upper left quadrant of the abdomen and in the left shoulder. The pain began three weeks before admission; it became severe the last few days and fever developed before admission. He had lost 15 pounds (6.8 Kg.) in the last month. He stated that ten years prior to this he had been struck by a plank across the epigastrium but that there had been few symptoms and he had recovered in a few days. One week before admission, he felt that he had injured himself diving in a pool. He laid great stress on both these injuries and repeatedly called attention to them.

His temperature on admission was 100.6 F., and he had a continuous low fever until the time of operation; the pulse rate was normal. Examination revealed a mass in the upper left quadrant of the abdomen; this was tender and conformed in every particular to an enlarged spleen. Because of this observation, detailed studies of the blood were made, but they revealed no abnormalities. Slight rigidity and distention and definite tenderness were present in the abdomen. The chest was normal. Roentgen studies included a complete series of gastrointestinal roentgenograms, an intravenous urogram and a pneumoperitoneal study. The mass demonstrated by these studies was interpreted as an enlarged spleen displacing the stomach toward the midline and the splenic flexure downward. There was no other abnormality in the stomach or the intestine; however, the left kidney was not visualized. As my associates and I observed the mass on various occasions, several of us felt that it was increasing in size. The left kidney could be palpated below and behind the mass, which in addition to becoming progressively slightly larger, became also more tender.

The impression was given that there was a slow hemorrhage from a trauma of the spleen, which was possibly well encapsulated, an enlarged spleen with a twisted pedicle (traumatic) or perisplenitis (traumatic). It was decided to operate. Through a left rectus incision an enormous retroperitoneal tumor was demonstrated; this had simply compressed and fixed the spleen against the ribs. On mobilization this tumor was readily delivered just over the kidney to which it was affixed. The kidney itself was grossly normal, except for a few cysts. The adrenal gland was incorporated in the capsule of the tumor, the main blood supply of which was derived from the renal vessels. The tumor and the kidney were removed intact. The tumor after fixation measured 19 by 16 by 14 cm. in diameter. On histologic examination it proved to be a myxosarcoma. The kidney was atrophied and the adrenal gland showed cortical hyperplasia, but neither revealed any evidence of neoplasm. After operation he was given roentgen therapy and at the time of writing has remained well, except for one minor attack of flatus attributed to an orgy of "hot dogs" and beer.

The emphasis on the trauma in this history led to the assumption that some trauma of the spleen due to the injury by the plank had been activated by the dive in the pool and had produced slow hemorrhage. While the dive may have been a factor in directing attention to the abdomen, it is probable, since there was no evidence of hemorrhage in the vicinity of the tumor, that the dive was in no way responsible for this

man having a retroperitoneal tumor. I leave it to the reader to decide whether trauma from a plank striking across the abdomen ten years before could cause a myxosarcoma originating in the retroperitoneal tissues.

The preponderance of pain in the later manifestations after abdominal trauma is important not only as a consideration in determining what surgical care the patient should receive but also as a potential basis of claims for indemnity. Since the legal status of pain is primarily determined by medical testimony, the physician should be alert to the importance of a proper evaluation of the role of trauma in arriving at a diagnosis.

A case may serve to illustrate one extreme of the wide variation in the relation of trauma to persistent pain in the abdomen.

CASE 2.—M. V., a 25 year old porter, was admitted for emergency treatment. He complained of severe pain in the abdomen with diffuse distention and tenderness. He stated that eight days before an iron bar had struck him on the head and the abdomen; he was vague as to what had happened since. The first diagnostic impression was "possible retroperitoneal hematoma." He was carefully observed for ten days, but complete physical, laboratory and roentgen examinations failed to bring to light any abnormalities. However, there was increasing evidence of what was finally diagnosed as a fear reaction. My associates and I were finally able to gain his confidence and convince him that he had escaped any of the serious ruptures he supposed should follow the injury. He was discharged but maintained under the care of a neuropsychiatrist and followed for several months, long enough to confirm that the whole trouble was essentially a fear pain. Certainly there never was evidence of any organic lesion, except flatus, that universal handmaid of the neurotic abdomen.

It must be remembered that severe strains of the muscles and blows on the abdomen may produce effects which depend on the fact that the abdominal cavity contains gas-filled organs, as well as solid viscera, with large blood vessels. The compressing action will vary according to whether the blow or the strain encounters a solid organ against a bony framework, such as the liver under the rib margin, or is exerted against the gas-filled compressible viscera.

Trauma from direct blows may involve any portion of the wall of the abdomen; it results in a varying degree of contusion with associated ecchymosis. This may involve the front of the abdomen but is more common over the lateral walls and the region of the loins. It is a well known fact that severe blows limited to a small area are more likely to result in extensive injury of the intestine and the mesentery than widespread trauma, which may result in lacerations of the liver, the spleen or the kidney. After a fall or a blow produced by a broad surface or a contusing force, such contusions may or may not be associated with contusions or ruptures of the viscera. As a rule, however, the patient experiences sharp pain with a moderate degree of shock; he recovers

from this with subsequent soreness of the wall of the abdomen followed by discoloration which varies in extent and is usually more marked along the iliac crest, where the blood tends to gravitate. Tenderness without marked rigidity and the absence of continued shock and hemorrhage are different from the initial symptoms of visceral injuries. There may be no evidence whatever of contusion of the wall of the abdomen in cases of severe injuries of the viscera, but shock and evidence of hemorrhage and peritonitis follow in fairly rapid order.

While in my experience there have been several instances of extensive hemorrhage after contusing injuries of the extremities, there has not been a single example of a severe hemorrhage in the muscles of the wall of the abdomen after contusion. On the other hand, there have been 2 instances of extensive hemorrhage in the right rectus muscle without any history of trauma.

CASE 3.—A. M., a 42 year old white woman, was admitted April 30, 1941 with the chief complaint of sharp pain in the right lower quadrant of the abdomen. She had been perfectly well until eight hours before admission. At that time (6 a. m.) she rolled over in bed and felt a sudden sharp stabbing pain in the right lower quadrant of the abdomen. This pain persisted constant and sharp. The last bowel movement on the previous day had been normal. The menstrual periods usually occurred every twenty-five to twenty-eight days and lasted for seven days. At the last period, one week before admission, the flow had been profuse with large clots; there had been no cramps; the previous period had been skipped, but the others had been regular. The patient had been examined one year before in a gynecologic clinic; at that time the uterus was slightly enlarged and anterior; there were no adnexal masses.

She was obese and slightly pale and was in acute pain. Her heart was enlarged 14 cm. to the left. Her pulse rate was × 80; her blood pressure was 154 systolic and 85 diastolic. There was a harsh systolic apical murmur. Palpation of the abdomen revealed a grapefruit-sized mass in the right lower quadrant, midway between the anterosuperior spine and the umbilicus. The mass was firm, extremely tender and easily felt, and the abdomen seemed to be freely movable over it. Examination of the pelvis and the rectum revealed a normal uterus and adnexa; the mass could not be palpated. The blood and the urine were normal.

The preoperative diagnosis was ovarian cyst with twisted pedicle, a degenerating pedunculated fibroid.

Dilation and curettage were performed. The rectus sheath was exposed through a lower midline incision and was found to be purple. The sheath was opened, and the entire right lower rectus muscle was observed to be necrotic and surrounded by about 6 ounces (177 cc.) of clotted blood. The right inferior deep epigastric artery was found to be actively spurting; it was clamped and tied. The peritoneal cavity was not opened. Closure of the incision was accomplished with plain 0 and chromic no. 1 catgut with a superficial drain. The patient was discharged in twelve days.

In this case, therefore, an extensive hematoma of the right rectus muscle simulating a pelvic tumor occurred without trauma and resulted from hemorrhage from the superficial epigastric artery without known cause.

The relation of trauma to lesions of the gastrointestinal tract has been carefully reviewed in the literature. Gerendasy and Crohn,[1] Eusterman and Mayo,[2] Gray [3] and others have reported ulcers of the stomach and the duodenum which followed direct abdominal trauma and were alleged to have resulted solely from such trauma. In a study of 121 cases of pancreatic cyst, Korte found a definite history of trauma in 27 per cent, such cysts being really peripancreatic with a collection of fluid caused by necrosis of the fat in the lesser omental sac.

Lévai investigated a series of 1,054 cases of appendicitis; in 9 there was a history of trauma from strain of lifting or from falls or blows. However, he expressed the opinion that the trauma activated rather than initiated the acute attack in a previously diseased appendix. There have been published reports of a few cases in which there were definite traumatic lesions, usually tears of the mesoappendix; these lesions correspond to the severe traumatisms found in the small intestine.

Aside from rupture, the evidence of severe trauma at operation includes a tear in the mesentery, areas of ecchymosis of the serosa or submucous hemorrhage. It is conceivable that in cases of so-called obstructive appendicitis trauma may distend the lumen of the appendix by forcing fecal material under pressure, thus simulating an attack in a previously diseased appendix. But since in the overwhelming majority of cases in which such a mechanism is present appendicitis occurs spontaneously without any trauma, it would be necessary to establish clearly that without previous symptoms signs of appendicitis followed directly and consecutively after the trauma.

In a total of 1,452 admissions I have been unable to find a single instance of a definite relation of trauma to the abdominal lesions of appendicitis, cholecystitis or gastric or duodenal ulcer. There were 9 cases in this series in which there were definite traumatic lesions of the abdomen; in 2 there was rupture of the bladder and in 2 there was severe contusion of the kidney; in 2 cases the diagnosis was retroperitoneal hemorrhage. In all of these cases the patients recovered. There was 1 case of rupture of the spleen and the jejunum, the history of which is as follows:

CASE 4.—R. C., a 7 year old boy, was struck across the abdomen by a stone balustrade when the platform on which he was standing collapsed. He was immediately brought to the hospital and admitted in severe shock; he was pale, and

1. Crohn, B. B., and Gerendasy, J.: Traumatic Ulcer of Duodenum and Stomach, J. A. M. A. **100**:1653 (May 27) 1933. Gerendasy, J.: Traumatic Peptic Ulcer, Am. J. Surg. **21**:12 (July) 1933.

2. Eusterman, G. B., and Mayo, J. G.: Traumatic Peptic Ulcer, Am. J. Surg. **26**:74 (Oct.) 1934.

3. Gray, I.: External Trauma in Relation to Ulcer of Stomach and Duodenum: Report of Five Cases, Ann. Int. Med. **7**:1403 (May) 1934.

his pulse rate was 150. His blood pressure was 90 systolic and 50 diastolic. The abdomen was becoming rapidly distended, rigid and markedly tender. There was no ecchymosis except a slight trauma of one foot. The blood counts were: hemoglobin, 70 per cent; red blood cells, 4,000,000; white blood cells, 38,300; polymorphonuclears, 81 per cent. Two hours later the blood counts were: hemoglobin, 63 per cent; red blood cells, 3,000,000; white blood cells, 29,000; polymorphonuclears, 91 per cent.

Operation revealed a laceration of the jejunum, which was torn across 2 inches (5 cm.) from Treitz's muscle, an extensive cracked eggshell laceration of the spleen and a tearing away of the splenic flexure. Rapid splenectomy and side to side intestinal anastomosis were done. The patient died a few hours later.

In reviewing a series of 57 cases of perforation of gastric ulcer I found no evidence of trauma in any instance. Perforation of the peptic ulcer did not seem to be precipitated by any factor related to the occupational activities of the patient. Perforations sometimes occurred after physical effort at work, but in the majority of cases they occurred while the patient was not actively engaged in any exertion, many occurring in the night. While in 1 or 2 instances in a large series of cases of appendicitis in the combined services at the Flower and Fifth Avenue Hospitals and the Metropolitan Hospital some traumatic factor has figured in the history, there has not been encountered a single example of appendicitis in which there was any evidence that trauma was primarily responsible.

A better understanding of the mechanism of abdominal pain and its distribution will be had by considering the structural components of the abdomen. These consist of a cavity surrounded by voluntary muscles supplied by the spinal nerves derived from the lower six thoracic and the first lumbar nerve and of the diaphragm supplied on its inferior surface by the phrenic nerve derived from the fourth cervical segment. The cavity contains viscera supplied largely by the splanchnic nerves with sympathetic parasympathetic fibers determining spasm or dilation of the lumens of the hollow viscera. Pain may result from inflammatory or traumatic irritation and is invariably associated with tenderness and rigidity. Further, pain may result from direct or distant irritation of the neural pathways. As a consequence, severe abdominal pain simulating a lesion may be caused by an extra-abdominal pathologic condition, just as the pain referred to the abdomen in cases of pneumonia in children simulates appendicitis and epigastric pain simulates peptic ulcer or cholecystitis in cases of angina; there is also the severe pain with hyperesthesia of the abdominal wall seen in cases of shingles or of lesions of the spine itself. The importance of careful control by obtaining a detailed history and making a careful physical examination of the symptom of pain is evident. Another factor to be considered is the variability of the threshold of pain according to the age and the sensitivity of the patient. These factors must be appraised in evaluating any claim

on the part of the patient that disability pain is the result of an occupational hazard, especially if few physical findings are evident. It has been said that the abdomen is the sounding board of the emotions. If the pain is the result of a traumatic lesion to which it is alleged to be related, this fact is usually susceptible of proof. In cases of abdominal pain, whether direct or referred, which is the result of an organic anomaly not itself the result of an occupational hazard nor attributable to trauma, claims for compensation can be established only by proving that the lesion would not in itself have caused the pain and associated symptoms without the particular exciting factor.

In cases of hernia, the factor of trauma is paramount in establishing a claim for compensation based on a history of the sudden onset of pain with or without a perineal bulge after strain or trauma sustained while working. This applies not only to the inguinal variety but to the other forms as well. Even in cases of incisional hernia (usually associated with intestinal or omental adhesions) such a history results in a claim for compensation. Such a case is that of a bartender who had had an incisional ventral hernia for twenty years after an appendectomy. After lifting a heavy case, he experienced severe pain, and the protrusion greatly increased in size. He was operated on a few hours later. In the omentum, which was adherent in the hernial sac, there was evidence of recent hemorrhage and of a new torsion of a segment of the omentum, probably the result of the trauma caused by the strain.

There is often a distinct and definite history of the appearance of a hernial bulge, of pain after a strain or of some trauma sustained while the patient was at work. In cases of postoperative intestinal adhesions the history often reveals the most typical symptom, pain induced by physical effort, straining or other factors involving trauma. In such cases, abdominal pain may be considered to have an important relation to claims for compensation. There can be no question of the definite relation of severe physical strain to hernia, and in these cases such strain may produce an increased protrusion or even incarceration. The degree of disability produced seems to justify a claim for compensation, even though surgeons recognize that the factor primarily responsible for the hernia is an anatomic defect. In cases of postoperative incisional hernia, in which adhesions play so important a part, abdominal strain resulting from certain occupational hazards or from injuries may produce a serious intra-abdominal lesion. The important point is that the lesion had not occurred before the trauma.

What is the emotional nervous background of the person seeking compensation and presenting pain as the prominent symptom? The answer to this question must be well considered. The burden of proof devolves on the doctor who denies the persistence of pain on the grounds of neurosis. In such cases disability entitling to compensation can be

denied only after a complete study has excluded all other possible explanations. In the search for a cause of pain in the abdomen sufficient to substantiate a claim for disability, roentgen examination offers visible evidence in contrast with the intangible evidence afforded by the history. It is in this group of cases that controversy most often arises. Tangible proof may settle what otherwise would continue as a merely academic discussion of the causation of the pain.

Pain, then, may result from many different factors; these should be evaluated in estimating whether the particular complaint is compensable. It should be borne in mind that if the pain is the result of the traumatic lesion to which it is alleged to be related, this fact is usually susceptible of proof. In cases of pain in the abdomen, whether direct or referred, the result of an organic lesion not itself the result of an occupational hazard or attributable to trauma, claims for compensation can be established only by proof that the lesion would not of itself have caused the pain and associated symptoms without the particular exciting factor.

30 Central Park South.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES
FRANK HINMAN, M.D.
SAN FRANCISCO
ALEXANDER VON LICHTENBERG, M.D.
MEXICO, MEXICO
ALEXANDER B. HEPLER, M.D.
SEATTLE
ROBERT GUTIERREZ, M.D.
NEW YORK
GERSHOM J. THOMPSON, M.D.
AND
JAMES T. PRIESTLEY, M.D.
ROCHESTER, MINN.
EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND
AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Surgical Procedures.—Rolnick and Singer [1] discuss contralateral massive collapse of the lung after operation on the kidney. This condition is rarely fatal and therefore often overlooked, particularly when minor degrees of involvement are present. If atelectasis persists for several days, it may be followed by infection of a mild pneumonic type, and then true postoperative pneumonia may be simulated.

This condition is often diagnosed as postoperative pneumonia because of the cyanosis, dyspnea and considerable increase of temperature above normal that almost invariably accompany atelectasis.

Atelectasis may follow any operative procedure, but it occurs most frequently after operation on the upper part of the abdomen. The direct etiologic factor is the accumulation of mucus and the retention of it within the bronchi followed by the formation of a mucous plug which blocks one or more bronchi.

Atelectasis may follow any type of anesthesia—inhalation, local or spinal. It also occurs when there is no increase of bronchial secretion.

1. Rolnick, H. C., and Singer, P. L.: Contralateral Massive Collapse of the Lung in Kidney Surgery, J. Urol. **45**:678-681 (May) 1941.

Preliminary administration of atropine may be a factor in producing the condition, since atropine does not diminish the secretion of mucus but merely concentrates it, thus helping to form a plug.

During and immediately after the operation, material in the larynx, the pharynx and the bronchi should be well aspirated. If this is done, the incidence of atelectasis will be markedly reduced.

Only a few instances of atelectasis after operation on the kidneys and on the upper portions of the ureters have been reported. In all, the condition occurred on the side opposite to that operated on; that is, the side on which the patient had been lying on an elevated kidney rest. With the patient in this rather difficult position, marked compression of that side of the thorax occurs during the entire operation, so that this is a site favorable to the development of atelectasis.

During the past ten to twelve years Rolnick and Singer observed 6 instances of atelectasis following operation on the kidneys and on the upper part of the ureters.

The enforcement of postural drainage is an essential factor in the rapid recovery of patients, along with the administration of expectorants and drugs which have an action opposite to that of atropine. Should the patient be gravely ill and should the long-continued spontaneous resolution of the atelectasis be too great a burden for the patient to bear, bronchoscopic removal of the plug of mucus is indicated. This is the most rapid and satisfactory method of relief of postoperative atelectasis. Bronchoscopic removal of mucous plugs is a routine procedure in some institutions.

Muschat [2] advises the use of balloon catheters for drainage after nephrostomy.

No adhesive plaster is required, because the filled balloon cannot come out. Introduction or replacement is painless and easy for the patient and the surgeon alike. Latex catheters are pliable and do not kink easily. They do not become lined with urinary salts as readily as the older kind. Removal and replacement are not complicated and can easily be accomplished by an attending nurse or even by a member of the patient's family. Filling the balloon is simple, and water or mineral oil can be used. Air should not be used, for it escapes within a few days, regardless of how tightly the inflation tube is secured. The wound remains clean, and after removal of the first granulation tissue, it continues to appear wholesome with little discharge.

If the patient is a man, a metal flask is placed in the regular hip pocket of the trousers, and the tube is placed within it after an opening has been cut through the shirt. This arrangement, and this one only,

2. Muschat, M.: Nephrostomy Drainage: The Use of Balloon Catheters, J. Urol. **45**:652-653 (May) 1941.

permits free motion, allows the patient to get up and sit down without discomfort and, what is more important, allows him to do these things without spilling.

McKenna and Kiefer [3] state that conservative operations have been done for some time in cases in which nephrectomy was impossible, such as, usually, those in which the opposite kidney was absent or functionless. The good results obtained in some of these cases have encouraged urologists to use these conservative procedures in more and more cases in which more radical procedures are not required.

A kidney the function of which has been held in abeyance by obstruction may be found at operation to have a large amount of apparently good renal tissue. The status of each kidney in the matter of infection should be studied completely in every case. Pyelography should be utilized to the fullest to get the most nearly accurate picture possible of the anatomic conditions present. When all the pertinent data have been accumulated, the surgeon must try to reach a decision as to the type of operation best suited to the condition at hand.

When the decision to do a conservative surgical procedure finally has been reached, the preoperative preparation must next be considered. The presence or absence of infection is a major consideration. Whereas nephrectomy, even with a badly infected kidney, usually can be done without gross contamination of the operative field, in many conservative operations the urinary tract must be opened, and any infective process present is spread to the large open surfaces of the wound.

At the time of operation, considerably more care must be exercised than is necessary with nephrectomy. Adequate exposure is more difficult to obtain but is even more essential than when the kidney is being removed. Meticulous attention to detail is necessary. Where the renal parenchyma is cut, hemostasis must be complete and effected in such a way as not to cause destruction of additional tissue. Nephrostomy and pyelotomy tubes must be accurately and carefully placed.

The patients on whom some conservative procedure has been done require more postoperative care and attention than patients who have had the kidney removed. This is true chiefly when some form of urinary diversion has been used. The drainage tubes require almost continuous watching by trained personnel.

Nephrostomy is, in McKenna and Kiefer's opinion, the most valuable of the conservative renal operations. At first used only as a means of permanent urinary diversion, it has been almost universally replaced in that role by ureterosigmoidostomy and cutaneous ureterostomy. At present it is used almost entirely for temporary short-circuiting of the urinary stream.

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3. McKenna, C. M., and Kiefer, J. H.: Conservative Renal Surgery, J. Urol. **45**:272-281 (March) 1941.

Seriously sick patients, whose ability to tolerate nephrectomy is doubtful, can undergo nephrostomy under local anesthesia if necessary. The freedom from toxic absorption, the improved urinary drainage and the direct access to the renal pelvis for lavage usually lead to a great improvement in the patient's general condition and often to a striking improvement in the local condition of the kidney as well.

In cases of obstructive anuria nephrostomy may be a life-saving measure, and in cases of this type in which the risk is bad the operation should precede attempts at direct removal of the obstruction.

For anuria of the nonobstructive type, McKenna and Kiefer have employed nephrostomy and decapsulation with success in about half the cases.

Wilhelm,[4] in discussing the McKenna and Kiefer article on conservative renal surgical procedures, states that in no field is conservatism more important than in the treatment of hydronephrosis caused by noncalculous obstruction at the ureteropelvic junction. He collected and analyzed the results of the 32 plastic operations on the renal pelvis and ureters which had been done at the Mount Sinai and Beth Israel hospitals in the twelve years prior to the time of his discussion. In cases of bilateral renal disease with uremia or with impending uremia, he makes it a practice, he says, to operate first on that kidney which apparently has the better function. If this kidney has been saved by performance of nephrostomy or, possibly, by a conservative plastic operation, the remaining side can be operated on with increased safety.

Anomalies.—Pierson and Honke[5] report a case of unilateral fused kidney with bilateral ureteral bifurcation afflicting a woman 58 years old who had persistent pyuria. She had been told on several occasions that the urine contained pus. Cystoscopic examination showed chronic cystitis to be present. Both ureteral orifices were in the normal positions. Catheters were passed without meeting obstruction in either ureter. A plain roentgenogram showed the left catheter to pass somewhat laterally to its normal course and the right catheter to cross the midline over the upper portion of the sacrum. Retrograde pyelograms demonstrated bifurcation of the left ureter at the junction of the upper two thirds and the lower third, with incomplete rotation of the entire left kidney so that the ureteral branch to the upper segment ran laterally to the lower and larger renal pelvis. The right kidney lay over the fourth and fifth lumbar vertebrae in the midline with a bifurcated ureter crossing from the right side.

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4. Wilhelm, S. F., in discussion on papers of Lowsley and Menning[24] and McKenna and Kiefer,[3] J. Urol. **45**:282-289 (March) 1941.

5. Pierson, L. E., and Honke, E. M.: Unilateral Fused Kidney with Bilateral Ureteral Bifurcation, J. Urol. **45**:682-684 (May) 1941.

Various urinary complications have been discovered in association with unilateral fusion anomalies. These vary from simple infection to additional types of congenital anomalies. Five reports in the literature definitely describe bifurcation of the ureter in association with unilateral fusion.

From this series, consisting of the case reported by Pierson and Honke in addition to 5 cases collected from the literature, a few observations may be obtained. Three of the patients died within the first ten months of life. Except for 1 patient whose sex was not stated, these 3 patients who died within the first ten months were males and included all the males in the series. The 3 female patients of the series lived to adult age. In 4 cases the fused mass lay on the right side, compared with 2 cases in which it lay on the left side.

In only 2 of the patients was the condition diagnosed before death. Pierson and Honke stated that in 1913 Rathbun found a left ureter bifurcated over the sacral promontory with right-sided fusion of both kidneys.

Ercole[6] reports 2 cases of horseshoe kidney in which he operated. Associated lithiasis was present in both. The approach in each case was made through an anatomic lumbar incision, a method which permits sufficient exteriorization of the isthmus.

In the first case, the fact that the two lower poles were in such close relationship that an isthmus hardly existed (the two being bound solidly together by a dense mass of parenchyma) and the additional fact that a lower polar vessel entered the kidney at the level of the isthmus led Ercole to give up the idea of performing symphysiotomy and to do instead simple pyelotomy for extraction of the calculus. This was the more logical procedure in view of the fact that the patient suffered only from the presence of the stone and not from any symptoms referable to the horseshoe malformation itself.

In the second case the isthmus, which likewise was composed of renal parenchyma, could be sectioned easily, and the stone could be extracted through an anterior pyelotomy opening. In this instance the preliminary placing of a clamp, with a view to severance of the isthmus in layers (which might be practicable if the isthmus were fibrous), would have constituted a definite disadvantage, since renal parenchyma is friable and may be easily torn by a clamp. Ercole also found that the placing of detached sutures for hemostasis, as Papin advised, is difficult, since, if the capsule is not resistant, it tears when the knot is tied. Ligature en bloc seems the simplest procedure and was carried out without complication in 4 cases in which Ercole used it.

6. Ercole, R.: Riñon en herradura y cirugía conservadura a proposito de nuevas observaciones personales, Rev. argent. de urol. **9**:343-351 (July-Aug.) 1940.

Foley [7] reports 6 cases of horseshoe kidney in which he has carried out symphysiotomy followed by nephropexy during the last ten years. In all but 1 of these cases (complicated by an incompletely removed stone) results have been completely satisfactory, after a period of from three to ten years. In a seventh case he did symphysiotomy for a unilateral fused kidney, also with good results. Of the 7 patients, 6 were women.

In all cases relief of pain was the chief objective. In 3 cases in which unilateral pain was present, division of the isthmus and relief of such pain were followed after a varied period by development of identical pain on the opposite side; complete relief was then provided by correction of the abnormal position of that side. In another case, originally mild pain on the opposite side gradually increased and was relieved one and a half years after the first operation by nephropexy on the second side. In 1 case of bilateral pain, division of the isthmus and nephropexy performed on only one side gave relief of pain on both sides. In the case of unilateral fused kidney, left-sided pain was relieved by symphysiotomy and nephropexy on the right. In nearly all the cases the character of the pain was fairly typical of that of pain of renal origin.

In all these cases it was possible to demonstrate obstruction and varying degrees of pelvic dilatation. In some infection of the upper part of the urinary tract and pyuria were present. In 2 cases there was unmistakable hydronephrosis, and in 1 of these the condition was complicated by stone. In none of the cases were there present merely the vague abdominal pain, constipation and other digestive disturbances that constitute the typical symptoms of horseshoe kidney disease without specific renal symptoms or renal pathologic change.

In cases in which the horseshoe kidney is observed accidentally (as, for instance, 1 in which the patient, without experiencing any kind of symptom, discovers the presence of an abdominal mass, representing the isthmus) there is no more reason to operate than there would be if an undiseased and symptomless kidney of normal form were present. In a second group Foley includes cases of horseshoe kidney in which definite frank pathologic change and symptoms of renal origin are present. In such cases it may be difficult to say what part in the symptom complex is played by the lesion and what part is played by the anomaly. Unless there are indications to the contrary, it may be best to proceed on the assumption that the associated lesion alone is responsible, to correct it surgically and to leave the anomalous relations undisturbed.

In a third group Foley places cases of horseshoe kidney in which symptoms of renal origin but not renal pathologic changes other than some degree of pelvic dilatation are present. The cases which he reports

7. Foley, F. E. B.: Surgical Correction of Horseshoe Kidney, J. A. M. A. **115**:1945-1951 (Dec. 7) 1940.

belong to this group. The various degrees of pelvic dilatation in such cases are caused directly by mechanical obstruction of the ureters occasioned by the anomaly, namely, the abnormal insertion of the ureter into the pelvis and contact of the ureter with the isthmus. On the basis of his experience in the clinical management of these patients, Foley concludes that the anomalous horseshoe kidney not affected by concomitant pathologic significant change may yet be productive of pain and other symptoms and of the insidious development of renal disease and that the kidney can be restored to normal anatomic relations with relief of symptoms and arrest of the insidiously developing renal disease by division of the isthmus and nephropexy on one or both sides.

Tumor.—Bugbee [8] states that the treatment of all renal tumor is nephrectomy if possible.

While the pathologic aspects of renal tumor are important in prognosis, a diagnosis of tumor is sufficient to warrant exploration of the kidney, unless metastasis is demonstrated, and even in the presence of metastasis an individual decision should be made in each case. In a case of the latter type operation and roentgen therapy for the metastasis represent the only chances for the patient and often are justifiable procedures. Large inoperable renal tumor can often be rendered operable by a preliminary course of roentgen therapy.

If the urologist waits for the appearance of a clearcut picture in which the diagnosis of renal tumor is certain, nephrectomy may prove to be only a palliative measure.

Painless hematuria probably is the most important early symptom of renal tumor. When suspicious deformities of the renal pelvis or calices are present in urograms, repeated examinations should be made, and if the results of such examinations are confirmed, exploratory operation on the kidney should be carried out.

The observation at operation of a kidney normal in size and contour should not dissuade the surgeon from removal of the organ if he has the courage of his convictions, based on his preoperative study of the case.

Braasch,[9] in discussing Bugbee's paper on exploratory operation for certain types of renal tumor, states that he has observed many patients for whom a diagnosis of renal tumor had been made previous to his examination on the basis of evidence obtained in the excretory urogram. An apparent deformity suggestive of tumor often is seen in the excretory urogram which more complete visualization in the retrograde pyelogram

8. Bugbee, H. G.: Exploratory Operation for Certain Renal Tumors, Tr. Am. A. Genito-Urin. Surgeons **33**:25-41, 1940.

9. Braasch, W. F., in discussion on papers of Dean and McCarthy,[10] Herman and Strumia,[20] Bugbee [8] and Wishard,[74] Tr. Am. A. Genito-Urin. Surgeons **33**: 57-60, 1940.

shows is not caused by tumor. Again, the excretory urogram, because of incomplete visualization, may not disclose any deformity, and the retrograde pyelogram will visualize it. A retrograde pyelogram should be made in every case in which the condition is doubtful. Careful scrutiny of minor details in the outline of the calices should be made routinely, and in case of doubt the condition of the patient should be checked subsequently by means of frequently made retrograde pyelograms. If these precautions are taken, renal tumor can be recognized in most cases, although occasionally an exploratory operation is necessary.

Dean and McCarthy [10] report a case of hemangioma of the kidney associated with diffuse hemangioma of the lower extremity. They make the report not only because of the rarity of each disease but also to emphasize the likelihood of such congenital vascular tumor affecting more than one part of the body of the same patient. In a study of 1,046 patients with tumor of the blood vessels it was noted that in a group of 9 patients suffering from diffuse hemangioma of an extremity, 2 had hemangioma of the viscera.

There is evidence in the literature that hemangioma of unusual situation or extent is often only part of a larger congenital pathologic complex. Angioma of the retina (von Hippel's disease) often accompanies angioma of the cerebellum, thus constituting still another disease complex known as Lindau's disease. Angioma of the central nervous system is frequently associated with cyst of the pancreas or kidney, whereas the common multiple hemangioma of the skin is often found with neurofibroma, lipoma or chondroma. Therefore, Dean and McCarthy believe that a tentative diagnosis of hemangioma of a viscus is warranted when a patient who has hemangioma of unusual extent suddenly experiences bleeding of uncertain origin.

Swan and Balme report a case of renal hemangioma and analyze 26 other cases of the lesion as reported in the literature. They found that in 80 per cent of the cases symptoms occurred before the patient reached the age of 40. The differential diagnosis was often difficult. Renal tuberculosis usually can be eliminated in the absence of dysuria, frequency of urination and pyuria. The absence of acid-fast bacilli and the presence of a normal cystoscopic picture of the mucosa of the bladder also aid in excluding this disease. Hemorrhagic nephritis is ruled out by the presence of unilateral bleeding and the absence of casts. Carcinoma of the kidney is rare before the age of 40, while renal hemangioma occurs most often before that age. Tumor of the kidney usually causes some pyelographic deformity, while in most cases hemangioma does not. In more than 40 per cent of the 27 reported cases the passage of blood

10. Dean, A. L., and McCarthy, W. D.: Hemangioma of the Kidney Associated with Multiple Hemangiomas, Tr. Am. A. Genito-Urin. Surgeons **33**:1-9, 1940.

clots from hemangioma caused lumbar pain or unilateral pain low in the abdomen similar to that caused by calculi in passage. However, renal and ureteral calculi, if present, can usually be found by roentgen study.

The principal symptom of renal hemangioma is hematuria. It is characteristically intermittent for days or weeks. Finally, it culminates in such profuse bleeding that an immediate operation is necessary to save the life of the patient. At operation the diseased kidney looks normal because the majority of the lesions are small and are situated beneath the epithelium of the pelvis, never involving the outer surface of the kidney. It is essential, therefore, to identify the diseased kidney by urologic methods before operation.

Bumpus,[11] in discussing the paper by Dean and McCarthy, reports 2 instances of hemangioma. One involved a patient he had treated in his student days in the Children's Hospital in Boston; it was a typical instance of poliomyelitis. No one had been able to make an accurate diagnosis until Dr. Harvey Cushing examined the child, found a small hemangioma on the face and said the child probably had hemangioma of the spinal cord. He operated the next week and found hemangioma of the spinal cord.

The second instance concerned a boy who had had hematuria first when he was 7 years of age. The bleeding had been extremely profuse and had required transfusion of blood a number of times. Bumpus followed the course of this patient at the Los Angeles County Hospital for two years. A 10 per cent solution of silver nitrate was injected to stop the bleeding. The boy tolerated this solution. There was one small filling defect in the lower calix of the left kidney, and it never changed. This patient was 14 years of age at the time of the discussion. Bumpus finally had to remove the lesion; no other hemangioma was detected in any other part of the body.

Froug[12] reviews 6 cases of liposarcoma of the kidney from the literature and adds 1 new case. His case is the fourth in which tuberculous sclerosis has been associated with this lesion. Perirenal insufflation of air with intravenous pyelography was a valuable aid in distinguishing renal tumor from perirenal tumor.

Calculi.—Boyd[13] reports on 4 patients with multiple small phosphatic stones and sand in the kidneys; 3 of them had poliomyelitis with rather

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11. Bumpus, H. C., in discussion on papers of Dean and McCarthy,[10] Herman and Strumia,[20] Bugbee[8] and Wishard,[74] Tr. Am. A. Genito-Urin. Surgeons **33**: 57-60, 1940.

12. Froug, C.: Liposarcoma of the Kidney: Review of the Literature and Case Reports, J. Urol. **45**:290-295 (March) 1941.

13. Boyd, M. L.: The Formation of Renal Calculi in Bedridden Patients, Tr. Am. A. Genito-Urin. Surgeons **33**:257-263, 1940.

extensive paralysis, and the fourth had suffered from a fractured femur which would not unite satisfactorily. The fourth patient had many rather small renal stones, all of which were passed after he had drunk large quantities of water and had lain three or four hours a day on his abdomen. One large stone would not pass through the ureter.

Multiple phosphatic stones probably can form in the kidney solely as a result of phosphaturia and lack of proper drainage due to position.

Naturally, all the other factors known to cause formation of renal stone may, and no doubt often do, exist in bedridden patients, and every precaution to prevent such formation, including drainage by posture, should always be taken.

Higgins,[14] in discussing Boyd's article, states that many factors are associated with the formation of stones in bedridden patients, about whom several interesting observations can be made.

First, the prolonged immobilization of the patients is accompanied by increased excretion of calcium. This can be demonstrated in a roentgenogram of the bones of the body.

Second, when a patient enters the hospital and is first immobilized, the reaction of the urine frequently is acid. After a short period of immobilization, the reaction of the urine invariably becomes alkaline. This change is influenced largely by the diet of the patient. An examination of the trays of patients who have been bedridden for an extensive period of time invariably will reveal that they eat more vegetables, are usually given large glasses of orange juice daily and only nibble at meat or those foods with an acid-ash base.

Third, constipation tends to develop among all these patients, and they are given large doses of peristaltic agents and liquid petrolatum. Higgins says that he has clinically demonstrated that if a patient is deficient in vitamin A and is given large doses of liquid petrolatum, he does not absorb the vitamin A concentrates. It is almost impossible to secure a normal biophotometric reading until the use of liquid petrolatum is discontinued.

Fourth, repeated catheterization of patients with injuries of the spinal cord eventually will introduce infection into the urinary tract. If a urea-splitting organism is introduced, the urine becomes strongly alkaline, and the p_H is elevated to a point at which precipitation of alkaline salts occurs.

Fifth, prolonged immobilization may foster stasis in the kidney.

Several steps may be taken, therefore, to prevent the formation of stones in bedridden patients, such as: (1) acidification of the urine by dietary means, that is, the inclusion of the acid-ash diet or acidifying

14. Higgins, C. C., in discussion on papers of Livermore,[41] Davis and Nesbit [47] and Boyd,[13] Tr. Am. A. Genito-Urin. Surgeons **33**:264-267, 1940.

agents and the omission, of course, of ammonium salts if a urea-splitting organism is present; (2) avoidance of the use of alkaline urinary antiseptic agents; (3) forcing of fluids; (4) changing of the patient's position in bed at frequent intervals; (5) administration of one of the various concentrates of vitamin A; (6) avoidance of administration of liquid petrolatum for extended periods; (7) careful observation of diet, so that if sufficient proteins are not taken, additional acidifying agents can be prescribed, and (8) exercise of extreme caution in catheterization to minimize the possibility of the introduction of organisms into the bladder.

Cases have been reported of the development in bedridden patients of stones which dissolved spontaneously when the patients became active again. Higgins says that he has on record a series of 9 patients in whom during the period of immobilization stones formed which were dissolved completely by means of dietary management.

Gutierrez [15] reported a case in which calculous pyonephrosis afflicting a boy 13 years of age was complicated by vesicoureterorenal reflux. The boy was cured by nephroureterectomy. This patient had been suffering from pyuria and occasional hematuria for the previous three years. Urographic study revealed a functionless state of the right kidney, calculous pyonephrosis and evidence of hydroureter and reflux, conditions rarely found together. Vesicoureteral reflux of urine is in itself a relatively infrequent finding. It is caused as a rule by congenital malformation but often by infection; both, in fact, may play a part in its causation, as they did in the present instance.

The necessity for complete urologic study of pyuria among children is pointed out. When the kidney is functionless and the ureter is diseased, it is important to remove both the kidney and the ureter, provided the function of the opposite kidney is good. According to the conditions that may be present, combined nephroureterectomy or ureteronephrectomy should be performed. Gutierrez says that he prefers combined ureteronephrectomy. However, for a young patient without much adipose tissue whose ureter is not so obviously diseased or dilated and whose kidney merits surgical exploration in the hope that it can be saved by a conservative procedure, although it has no function as revealed in the excretory urogram, exposure of the kidney should be done first and then aseptic nephroureterectomy should be carried out. To leave an infected, dilated or obstructed ureter in its place is to invite complications. When vesicoureteral reflux is present, if the ureter is not removed with the kidney, lumbar urinary fistula or other complications almost certainly will develop.

15. Gutierrez, R.: Calculous Pyonephrosis in a Boy Thirteen Years of Age, Complicated with Vesico-Uretero-Renal Reflux, Cured by Nephroureterectomy, Urol. & Cutan. Rev. **45**:117-120 (Feb.) 1941.

In cases in which intravenous urograms disclose a functionless calculous pyonephrotic kidney, if there is assurance of normal function in the kidney of the opposite side and if a good cystogram shows the condition of the bladder, routine cystoscopic examination, and the making of retrograde pyelograms may not be necessary. This is the more so if roentgenograms show that a calculus is impacted at the ureteropelvic junction of the offending kidney and if no excretion can be obtained from the same kidney in the excretory urograms. In such a case, complete blocking produced by stone is obvious and there is no need to distend the renal pelvis by injecting the ureter from below. Among children intravenous urography together with the making of a cystogram or a cystourethrogram is a much simpler procedure than cystoscopy. The latter should be done only if absolutely indicated.

Hydronephrosis.—Shupe [16] states that conservative surgical treatment of hydronephrosis may be attempted in the presence of all degrees of ureteropelvic obstruction, whether infection is present or absent and even if the function of the kidney is much diminished. Postoperative drainage of the pelvis is necessary whether infection is present or not. By means of conservative plastic surgery, patients may still retain both kidneys and be relieved of pain and infection for periods of three to six years and possibly permanently.

Quinby,[17] in discussing Shupe's article on conservative surgery for renal pelvic obstruction, calls attention to the fact that the blood supply of the upper end of the normal ureter (that portion adjacent to the renal pelvis) is just as ample as the blood supply to any other part of the ureter. Although there has been no hesitancy on the part of surgeons to carry out plastic procedures on the lower end of the ureter, there seems to be still in the minds of many surgeons a hesitancy to rely on the natural blood supply of the upper end of the ureter to permit quick healing if the ureter is severed from the renal pelvis. Quinby's own experience in operations in which the ureter was entirely divided from the renal pelvis is now sufficient to demonstrate this point, namely, that the blood supply of the normal ureter is adequate to allow perfectly smooth healing after complete division followed by the reimplantation of the severed end. In a good many cases of this type there has been antecedent infection which may have died out by the time of operation, so that even though the tissues may be sterile, definite formation of scar tissue is left at that area. When this exists, it does not seem logical to attempt a plastic operation through the old scar, because, regardless of

16. Shupe, T. P.: Conservative Surgery in Renal Pelvic Obstruction, Tr. Am. A. Genito-Urin. Surgeons **33**:101-114, 1940.

17. Quinby, W. C., in discussion on papers of Colby [21] and Shupe,[16] Tr. Am. A. Genito-Urin. Surgeons **33**:115-121, 1940.

what may happen after the operation, healing can be accompanied only by further formation of scar tissue.

For these reasons Quinby chooses to avoid such an area entirely in the attack on the obstruction. He has therefore strongly advocated complete severance of the ureter followed by implantation of it into whatever other portion of the pelvis seems advantageous from a mechanical point of view. True, the whole pelvic wall in instances of considerable dilatation will exhibit hypertrophy in some degree, but it is not scarred. In cases in which free transplantation of the upper end of the ureter has been made into some other portion of the pelvis, the operation is much simpler and more logical than any of the rather complicated plastic procedures.

Pseudohydronephrosis.—Johnson and Smith [18] reported a case of perirenal pseudohydronephrosis with calcification. A woman 41 years old entered the hospital complaining of a symptomless mass in the left side of the abdomen. It extended from the costal margin to below the umbilicus, filled the flank and extended to the midline anteriorly. Thirty-seven years before, a wagon had passed over her abdomen and flank; from this injury she had finally recovered. Results of a physical examination were negative except for this large, nontender, firm, nodular, rounded and immobile tumor.

Complete urologic study revealed a calcified multicystic mass in the vicinity of the left kidney. The left ureteral catheter was obstructed at 20 cm. The contrast medium would not pass above this point, and urine was not obtained.

At operation, a multilocular calcified cyst containing amber-colored fluid was found directly under the transversus abdominis muscle. It communicated with the pelvis of an atrophic hydronephrotic kidney. The cyst and the remnant of the kidney were removed.

Perirenal pseudohydronephrosis can develop after renal trauma only when complete laceration through the renal parenchyma, as well as ureteral obstruction, obtains. This injury allows the extravasation of both blood and urine into the perinephric space, limited by the perinephric fat and Gerota's capsule. After bleeding ceases, the urine continues to pass out through the renal wound because of the ureteral block, which will not allow the parenchymal tear to heal, and progressive hydronephrosis is the rule.

In the presence of the urine the perirenal fat becomes fibrosed and finally hyalinized. For this reason perirenal fat is not found between these cysts and the transversus abdominis muscle, and these cysts are not lined by epithelium.

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18. Johnson, C. M., and Smith, D. R.: Calcified Perirenal Pseudohydronephrosis, J. Urol. **45**:152-164 (Feb.) 1941.

Pathologic calcification may occur in any devitalized tissue in the body, and it is not surprising that it should occur in the hyalinized avascular wall of the cyst. In this regard, however, this case is unique in the literature. Other cases of calcification about the kidney after trauma have been published, but proof is lacking as to the exact condition present. Certain intrarenal lesions lead to pathologic calcification, and the walls of solitary cysts not uncommonly contain calcium, but complete urologic investigation easily distinguishes these lesions from calcified perirenal pseudohydronephrosis.

Surgical excision of these calcified tumors is not advisable unless symptoms are bothersome, because of the marked adherence of the walls of such tumors to the peritoneum, muscle and rib cage.

Pyelonephritis.—Prather and Sewall [19] discuss the relation of pyelonephritis to toxemia of pregnancy.

The data for their paper are based on the observations and records of 72 patients who had pyelonephritis and were pregnant in the period from 1930 to 1939. Records of only those patients who were pregnant one or more times subsequent to the pregnancy complicated by pyelonephritis are used. Of the 72 patients, 42, or 58.3 per cent, were primiparas; 30, or 41.7 per cent, were multiparas. Seventy had pyelonephritis during pregnancy; 2 had acute pyelonephritis immediately after delivery, while they were still in the hospital. Forty-three, or approximately 60 per cent, were in a febrile phase while they were in the hospital, leaving 29, or 40 per cent, in an afebrile subacute stage at the time of observation.

The records of these patients suggest a history of pyelonephritis among 16.6 per cent; half of these had the disease during a previous pregnancy, and the remaining half had had pyelonephritis before the onset of any pregnancy.

Roentgen data were obtained concerning 55 patients, 26 of whom had had intravenous pyelographic study and 29 of whom had had retrograde roentgen study. The dilatation of the ureters and the pelves and the ureteral kinks were not extraordinary to any one familiar with urologic changes during pregnancy. The renal and ureteral dilatation in the subsequent pregnancy never exceeded that encountered during the time of the first occurrence of pyelonephritis, irrespective of whether the subsequent pregnancy was normal or complicated by recurrent pyelonephritis or toxemia. In general, patients with toxemia appear to have less ureteral and pelvic distortion (as revealed by intravenous pyelograms) than normal women.

Of the 72 patients with pyelonephritis, 47, or 65.28 per cent, completed a normal pregnancy at a later date. The interval between the

19. Prather, G. C., and Sewall, W.: Relation of Pyelonephritis in Toxemias of Pregnancy, Surg., Gynec. & Obst. **72**:781-786 (April) 1941.

pyelonephritis that had arisen during pregnancy and the normal pregnancy varied between one and nine years, the average interval being three and sixty-two hundredths years. Frequent recordings showed the blood pressure to be normal during the subsequent pregnancy in all 47 cases. In 34 of the patients blood pressure during the normal later pregnancy was about the same as it had been during the pregnancy that was complicated by pyelonephritis; in 13 patients it averaged lower than it has been during the uncomplicated pregnancy.

Of the 72 patients who later returned pregnant to the hospital, 9, or 12.5 per cent, were afflicted with toxemia.

Prather and Sewall conclude that pyelonephritis is not a cause of toxemia of pregnancy.

Hemorrhagic Cysts.—Herman and Strumia,[20] discussing primary hemorrhagic cysts of the kidney, state that these cysts are rare in surgical practice. Their series was made up of 6 cases in which the patients were subjected to operation. The cysts were of the simple retention type, and 3 could be classified as primarily hemorrhagic. In each of these cases the symptoms and the pyelographic observations led to the erroneous diagnosis of neoplasm. Either type of cyst may come to the attention of the surgeon because of symptoms arising from a complicating lesion, such as stone or inflammation, but in the present series all the patients had gross renal hematuria, accompanied in 1 case by pain. Hemorrhage in a case of simple retention cyst of the kidney probably is caused by rupture of distended veins in the walls of certain calices, the distention arising as a result of interference with the circulation. Certain cysts of the type under discussion may be treated successfully by segmental resection. This was the means employed in 1 case of simple cyst in the series reported by Herman and Strumia. However, the occurrence of gross bleeding from a kidney presenting somewhat diminished function and pyelographic distortion highly suggestive of neoplasm frequently leads the surgeon to remove the kidney, notwithstanding the benign appearance of the visible portions of the cyst.

Herman and Strumia summarize their observations by saying that primary hemorrhagic cysts are of variable causation and mechanism, as reflected in the great variety of pathologic observations which are made, and that although they are dependent on diseased blood vessels the predisposing lesion is not necessarily aneurysmal.

Tuberculosis.—Colby [21] states that patients suffering from renal tuberculosis are so benefited by treatment in a sanatorium before opera-

20. Herman, L., and Strumia, M.: Primary Hemorrhagic Cysts of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **33**:11-23, 1940.

21. Colby, F. H.: Renal Tuberculosis and Sanatorium Care, Tr. Am. A. Genito-Urin. Surgeons **33**:95-99, 1940.

tion that such treatment should be a part of the routine care. Operation is seldom advisable until the patient shows evidence of increased resistance to the disease. This service is rendered best by institutions in which care is devoted to extrapulmonary tuberculosis, but few communities have hospitals of this character.

Renal and genital lesions complicate tuberculosis of bone more frequently than is generally supposed, and constant albuminuria is an early indication that the kidney may be involved. At the Lakeville State Sanatorium, Middleboro, Mass., the inoculation of guinea pigs has been a more reliable laboratory procedure for the detection of tuberculosis than the taking of material for cultures.

Baggenstoss [22] states that healed miliary tubercles of the kidney were found incidentally at necropsy in 9 cases. Similar miliary tubercles with definite evidence of regression but slight histologic evidence of activity were found in 6 additional cases. In none of these cases was there any clinical evidence of either renal or pulmonary tuberculosis. These cases add to the evidence that renal tuberculosis heals when circumstances are favorable. It is probable that healed tubercles of this type occur more frequently than the small number of cases reported indicates.

Keyes [23] reports 6 cases in which cutaneous ureterostomy (in 1, bilateral) was performed for tuberculosis. In these cases the operations of nephrectomy and contralateral ureterostomy were performed: in 1 case they were performed simultaneously; in 1 case ureterostomy was done before nephrectomy; in 4 cases it was done after nephrectomy, at intervals of two, four, five and six years.

At the time of Keye's report (1940), 3 patients had given no suggestion of tuberculosis in the kidney or ureter since ureterostomy. These patients (except 1 who needed meatomy) had made no complaint and needed no attention to the ureter during a postoperative interval of three (in 1 case) to nineteen (in 2 cases) years. They did not need a catheter. Two of them kept themselves dry by night as well as by day, and the third, a surgeon, was "too much enamoured by his homemade apparatus to bother about his wet nights." Three patients were well and free from the odor from the urine. One married since undergoing ureterostomy; 1 bore a child, something she had previously been deemed incapable of doing.

The 3 patients who had tuberculosis of the remaining kidney were wearing an indwelling catheter at the time of Keyes's writing. The 2 who were followed had phosphatic stone within three years after ureter-

22. Baggenstoss, A. H.: Healed Tuberculosis of the Kidney, J. Urol. **45**:165-175 (Feb.) 1941.

23. Keyes, E. L.: Cutaneous Ureterostomy for the Relief of Intractable Bladder Tuberculosis After Nephrectomy, Tr. Am. A. Genito-Urin. Surgeons **33**:169-174, 1940.

ostomy. Yet, perhaps because there was good ureteral drainage, the progress of the renal lesions seemed slow, and other tuberculous lesions tended to subside. One of these patients died thirteen years after ureterostomy.

This report justifies no conclusion other than that cutaneous ureterostomy may bring long life to the patient tortured by a tuberculous bladder.

Rupture.—On the basis of experimentation with animals and clinical experience with human beings, Lowsley and Menning [24] conclude that early operation, evacuation of blood clots and production of hemostasis by means of pieces of fat held in place by ribbon gut fixed in the capsule will be followed by less destruction than failure to treat renal traumatism. Any patient who has a history of trauma and who has had hematuria for more than twenty-four hours should have the benefit of an exploratory operation, because such a procedure is now considered to be much more conservative than hopeful waiting.

Engel [25] states that Lowsley and Menning have departed from the usual conservatism in advocating exploratory operation in every case of suspected rupture of the kidney in which the bleeding persists for more than twenty-four hours. Their own statistics permit question of the wisdom of this attitude, for of 36 patients seen by them since 1920, 17 were operated on, with 6 deaths, a mortality rate of 35 per cent; whereas among 19 patients not operated on there was only 1 death, a mortality rate of only 5 per cent. Engel favors a policy of watchful waiting for traumatic rupture of the kidney, especially the subcapsular type, reserving operation for those patients who have severe extracapsular hemorrhage or for the occasional patient for whom watchful waiting must be abandoned because a sudden turn of events threatens his life. Of 17 patients seen in Engel's clinic since 1922, only 2 were operated on; both underwent nephrectomy.

Wood [26] states that the main problem in a case of injury to the kidney is that of determining the extent of the injury and the time at which to operate. A considerable number of patients who suffer trauma to the kidney will recover after conservative treatment. For this reason Wood questions whether or not all patients who have hematuria of no more than twenty-four hours' duration should be subjected to operation. The patients who need immediate operation are those who have severely injured kidneys, which are usually completely ruptured. The main

24. Lowsley, O. S., and Menning, J. H.: Treatment of Rupture of the Kidney, J. Urol. **45**:253-271 (March) 1941.

25. Engel, W. J., in discussion on papers of Lowsley and Menning [24] and McKenna and Kiefer,[3] J. Urol. **45**:282-289 (March) 1941.

26. Wood, A. H., in discussion on papers of Lowsley and Menning [24] and McKenna and Kiefer,[3] J. Urol. **45**:282-289 (March) 1941.

difficulty is to determine the time at which to operate on these patients. In Wood's experience, they do better if allowed to recover from the immediate shock with supportive treatment. If operation is carried out, it should be deferred, if possible, for at least three or four days.

URETER

Injuries.—Smith and Smith [27] discuss transureteroureteral retroperitoneal anastomosis in man. They report 2 cases in which the operation was successful.

Their procedure is as follows: Prior to operation a ureteral catheter is passed up the good ureter for a reason that will presently be made clear. An incision is made in the midline below the umbilicus, and the abdomen is opened in the usual manner. The patient is placed in the Trendelenburg position, the intestines are packed off, and the ureters are identified. An incision is then made in the posterior parietal peritoneum over each ureter, a short distance above the brim of the pelvis. The ureter on the injured side is freed over a distance sufficient to permit it to swing freely over to the opposite ureter. The injured ureter is doubly ligated with catgut and divided. Then, with a Kelly clamp, a tunnel is made under the posterior parietal peritoneum. The ligated ureter is then drawn through the tunnel and brought to lie alongside the noninjured ureter in such a manner that no tension is present. Anchor sutures of no. 2 chromic catgut are placed approximating the two ureters for a distance of 2 or 3 cm. Longitudinal incisions are made in each ureter along the borders of approximation. The posterior layer of the anastomosis is then closed with interrupted sutures of no. 000 chromic catgut. Once the posterior layer is laid, the catheter which was inserted before operation is drawn down until the tip can be grasped and brought out through the anastomosis. Two no. 7 or no. 8 French ureteral catheters are fixed to the tip of the catheter. The original catheter is then drawn out, so that the two catheters are carried with it until these can be grasped from the outside. The proximal end of the one catheter is placed into the pelvis of the normal kidney, and that of the other catheter is inserted into the renal pelvis of the injured side. The purpose of this procedure is to divert as far as possible the flow of urine over the site of anastomosis. After this, the anterior suture line is put in place, completing the anastomosis. At this point sutures are placed in both ureters distally and proximally to the anastomosis and are sutured to the fascia of the psoas muscle. This is done to relieve further any tension that may be exerted on the anastomosis. A stab wound is made in the side, and a soft rubber drain is

27. Smith, P. G., and Smith, D. P.: Ureteral Injuries and Their Management, Tr. Am. A. Genito-Urin. Surgeons **33**:175-183, 1940.

brought down to, but not in contact with, the anastomosis. The openings in the posterior parietal peritoneum are closed with continuous sutures of catgut. The abdomen is then closed in the usual manner. The ureteral catheters are fastened to the inner aspects of the patient's thighs and are left in place for four or five days.

Stone.—Bergman [28] reports 9 cases of vaginal ureterolithotomy; in 8 of these the operation was successful.

He states that stones lodged in the vicinity of the ureterovesical juncture may be extremely difficult to remove; this is indicated by the number of procedures which have been advocated for attack on calculi lodged in this region. Bergman cites Lower's statement that of the four avenues of approach to ureteral stones lodged within the pelvis, namely, the vesical, the rectal, the sacral and the vaginal, the latter has distinct advantage in that it is the simplest, easiest for the surgeon to utilize and least disturbing to the patient. The vaginal route has a notable superiority over the abdominal route, particularly when adiposity and adhesions are marked. Anatomically, the approach from below is not only more logical but also simpler, and it is accompanied by a minimal degree of shock. Drainage is dependent, and the possibility of development of external incisional hernia is excluded. Morris is quoted as saying that the lower part of the ureter passes

> from ⅛ to ½ inch above and to the outer side of the lateral fornix of the vagina, crossing beneath the broad ligament, and uterine artery at the side of the neck of the uterus, from which it is separated by loose connective tissue. The distance between the cervix uteri and the ureter is ¾ to 1 inch. The ureter terminates at the base of the bladder 1¾ inches from its fellow of the opposite side. It lies in front of the anterior vaginal wall, ¼ to ½ inch below the anterior fornix.

Bergman states that he places the patient in the extreme lithotomy position. While the patient is under anesthesia, an attempt is made to palpate the stone through the vagina. If orientation is difficult, a catheter inserted in the ureter may serve as a guide. Flexible retractors are then placed into the vagina. The cervix is grasped with a tenaculum forceps and traction is exerted to gain better access to the stone by bringing the base of the bladder and ureter into the field.

The incision is transverse, usually 3 or 4 cm. long, and is made anterior and lateral to the cervix through the mucous membranes of the vagina; thus it is made directly over the stone, if the stone is palpable. The incision is further deepened with blunt dissection by forceps, and the finger then introduced should palpate the stone. To avoid serious bleeding it is important to remember that the uterine artery will be found above and medial to the ureter. The ureter is then grasped with an 8 inch (20 cm.) Babcock forceps placed above the calculus, if possible,

28. Bergman, R. T.: Vaginal Ureterolithotomy, J. Urol. **45**:176-185 (Feb.) 1941.

to prevent the calculus slipping up the ureter. With the ureter thus exposed, a longitudinal incision is made through the wall of the ureter and the calculus removed. Fine chromic catgut is used to suture the ureteral incision, and the vaginal incision is left open for drainage.

Unless the calculus is impacted, it may slip up the ureter beyond reach when removal is attempted. This has occurred in 5 of Bergman's cases. In 3 of these cases the Johnson basket dislodger was successfully utilized by passing it through the vaginoureteral incision and engaging the stone, which was then easily removed from the dilated ureter.

The ureter is below and lateral to the uterine artery, so that dissection carried in a more lateral direction should avoid injury to this vessel.

Postoperative ureteral drainage by catheter has been used in most of Bergman's cases but has not seemed to diminish appreciably the transient postoperative leakage of urine through the incisional orifice. In his series, the shortest duration of urinary leakage through the incision was four days, and the longest period (the patient had experienced severe hemorrhage) was one in which drainage persisted for ten weeks before the incision closed spontaneously. In most of the cases, drainage endured from one to three weeks after surgical intervention.

Transplantation.—Stevens [29] states that reports concerning 38 patients who have survived ureterointestinal implantation for nonmalignant conditions are to be found in the literature; 11 of these patients had survived for more than twenty years. Two patients whose cases are recorded in Stevens' paper bring the figure for those reported living more than twenty years to 13. The number of patients who have lived this long after the operation probably is much larger but unrecorded.

All but 1 of the 38 patients referred to were victims of exstrophia of the bladder.

A report is given concerning a man living for more than forty-three years after operation, performed by the late Dr. George R. Fowler.

Brief summaries of the conditions of the 7 patients whose ureters were placed in their bowels on account of incontinence referable to nonmalignant conditions, are appended to Stevens' report: 2 died after six years of life; the others were living four to twenty-nine years after operation at the time of Stevens' report.

BLADDER

Tumor.—Watson and Herger [30] present the methods of treatment and the results in 445 cases of tumor of the bladder. An attempt was

29. Stevens, A. R.: Longevity Following Uretero-Intestinal Anastomosis, with Report of Cases, Tr. Am. A. Genito-Urin. Surgeons **33**:157-167, 1940.

30. Watson, E. M., and Herger, C. C.: Carcinoma of the Bladder: A Correlation of the Pathological and Clinical Data as a Basis for Treatment, J. Urol. **45**: 331-336 (March) 1941.

made to correlate the clinical picture and the pathologic observations, so that a basis for choice of treatment might thereby be established. Operation, radiation therapy and electrocoagulation were used either alone or in various combinations. Statistics are presented for two five year groups. In the first group, 28 per cent of the patients with papillary tumor remained well for more than five years, while 12 per cent of those with solid infiltrating tumor remained well for more than five years. In the second five year group, Watson and Herger were able to obtain disappearance of papillary tumor in 43 per cent of the patients for periods of from one to four years, although of the patients with nonpapillary solid infiltrating tumors only 10 per cent remained alive and well for periods of from one to four years. It is their opinion that results in the second group will be improved, partly because of advances in the technics of operation and radiation therapy and partly because of a better adaptation of the methods of treatment employed in the different clinical and pathologic groups.

Colby [31] states that tumor of the bladder treated with 1,000,000 volts of external radiation, constant potential, has responded better than that treated with lower voltage. Well marked regression of the tumor has occurred in about half the cases in which this method of treatment has been employed, and at least temporary disappearance of the tumor has been secured in about a third of the cases. In the present experimental stage, it is doubtful whether this agent is curative, and it should not be regarded as a substitute for surgical treatment. Symptoms, such as bleeding and painful and frequent urination, were relieved in about half the cases.

Leukoplakia.—Thompson and Stein [32] report a series of 34 cases of leukoplakia of the urinary bladder. They observed that although in most instances there were no cardinal symptoms of leukoplakia, the patients complained of suprapubic pain and tenderness unassociated with voiding. In most cases the diagnosis was verified by biopsy, and the authors stress the necessity of such an examination. The disease is more common among men and is most frequently situated around the trigone of the bladder. In every case of leukoplakia, associated pyuria and excretion of cocci were observed. Treatment consisted of fulguration of the leukoplakial portions either by suprapubic or cystoscopic approach. The latter method was considered preferable because the extent of the leukoplakial lesion can be recognized with a reasonable approximation of accuracy with the cystoscope, while it is comparatively difficult to delineate the lesion with the unaided eye through a suprapubic incision.

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31. Colby, F. H.: Evaluation of the Supervoltage Treatment of Bladder Tumors, J. Urol. **45**:337-341 (March) 1941.

32. Thompson, G. J., and Stein, J. J.: Leukoplakia of the Urinary Bladder: A Report of Thirty-Four Clinical Cases, J. Urol. **44**:639-649 (Nov.) 1940.

Thompson and Stein employ an interesting method of treating the lesions: They first fulgurate a line around the periphery of the entire lesion and then proceed with superficial fulguration within this zone. This is necessary because repeated distention of the bladder produces a fading of the margins of the lesion. The results of this treatment have been satisfactory.

The combination of leukoplakia and carcinoma was found in only 2 instances in this series. The authors point out that leukoplakia occurs in the stratum corneum, the cells of which are dead. These cells have lost all power to react to stimuli, and it is impossible for a malignant process to develop within the cornified or leukoplakial region.

Obstruction of the Neck of the Bladder.—Trabucco [33] made a comparative study of pathologic conditions of the neck of the bladder in men and women. Although such pathologic aspects have received recognition and close attention in men from time immemorial, it must be admitted that the study of diseases of the neck of the bladder in women is still in its infancy and that the causes of such diseases too frequently remain unrecognized.

In women acute retention of urine seems to predominate at the outset, and retention becomes irreducible, requiring permanent use of a catheter and surgical intervention. In men, on the contrary, the first symptom is dysuria, signalized by retardation of the urinary stream. This is premonitory of retention. Trabucco thought that dysuria is present in both men and women but that in the latter, for obvious reasons, it is more difficult to establish the fact that it is present.

The embryonic anatomy of the two sexes is reviewed, and it is pointed out that in women the muscle of the vesical neck is not so evident as it is in men; it is broader and is directed downward, occupying nearly half the urethra in women, resulting in a certain anatomic difference of some importance.

In men two basic types of the disease may exist: (1) the circular, which embraces the entire contour of the neck, and (2) that which is localized in the so-called lower lip and is confined there. The former is chiefly traumatic, but occasionally it is congenital. The second type is again subdivided into fibrous and glandular changes. The fibrous subtype may be congenital yet may not reveal itself until senile changes of an inflammatory nature bring it to light. Acquired sclerosis of the so-called lower lip of the neck of the bladder, which is much more common than is supposed, is referable especially to prostatitis and seminal vesiculitis caused by one or another infective agent. The glandular type of change in the lower lip of the neck of the bladder in

33. Trabucco, A.: Estudio comparativo de la patología del cuello vesical en el hombre y en la mujer, Rev. argent. de urol. 9:355-361 (July-Aug.) 1940.

men is due to glandular hypertrophy. Home's lobe above the neck of the bladder in the region of the trigone and the subcervical glands of Albarran, which ordinarily remain in a state of latency, may undergo endocrine or other changes which cause them to increase in size so that they exert pressure on the muscle of the vesical neck and gradually cause destruction of it. Likewise, inflammatory changes may lead to invasion and destruction of the muscular elements by connective tissue. Retention then results from lack of kinetic force in the lower lip due to destruction of the latter's motor portion.

In women it has been considered that changes in the neck of the bladder must be caused solely by inflammatory hyperplasia of connective tissue or by change of the musculature into fibrous tissue. Theoretically, in women the vesical neck and the subcervical part of the urethra have no glands. Numerous works and histologic studies have seemed to prove this. The shortness of the urethra in women and its close proximity to infected zones readily account for the frequency with which the neck of the bladder becomes inflamed, especially among women of advanced age. Nevertheless, Trabucco recently encountered a young woman in whom retention of urine demonstrably was caused by typical glandular hypertrophy of elements situated in the lower lip of the neck of the bladder, an observation confirmed by histologic study.

Trabucco points out the importance of this observation. It might be more nearly accurate to say, not that the female urethra contains no glands, but that it contains no visible glands. That glands have not been found does not prove that they do not exist. It must not be forgotten that in women the elements of the lower lip of the neck of the bladder are derived embryologically from a special formation similar to that in men and that in this formation there exist glands in a state of latency. Although normally these glands atrophy in the female, it is wholly possible that special endocrine changes affect some women so that these glands persist, leading to glandular hypertrophy comparable to the changes in men that produce various types of adenoma.

Stone.—Emmett [34] states that vesical calculi of the ordinary type may reach enormous proportions. Some stones have been reported which were so large that they filled the entire bony pelvis. It may be impossible to remove such a stone through the usual suprapubic incision unless the stone is first broken into smaller pieces. On the other hand, it is relatively uncommon to encounter large calculi of the jackstone type in the bladder. Most jackstone calculi vary from 0.5 to 2 cm. in diameter.

Emmett reports the following case of large stone: A man 60 years of age stated that for ten years he had suffered from moderate urinary

34. Emmett, J. L.: Unusually Large "Jackstone" in the Urinary Bladder: Removal by Litholapaxy, Proc. Staff Meet., Mayo Clin. **16**:269-270 (April 23) 1941.

symptoms. Digital examination of the prostate gland through the rectum revealed enlargement, grade 2. Roentgenograms of the kidneys, the ureters and the bladder revealed the shadow of a stone in the left renal pelvis and the shadow of an unusually large jackstone calculus in the vesical region. Cystoscopic examination revealed a free jackstone calculus, 5 or 6 cm. in diameter, a diverticulum about 3 cm. in diameter arising from the lower part of the right lateral wall of the bladder and grade 2 enlargement of the lateral lobes of the prostate gland. With the patient under light spinal anesthesia, the stone was crushed with a lithotrite, and the fragments were evacuated. The stone was extremely hard. Some of the fragments washed into the diverticulum, and it was necessary to introduce the beak of the cystoscope into the diverticulum to remove them. A urethral catheter was left in place for drainage. Four days later, with the patient under light spinal anesthesia, the prostatic obstruction was removed by means of transurethral resection. Chemical analysis of the stone proved it to be calcium oxalate.

Crance [35] reported a case in which he removed a giant vesical calculus with obstetric forceps. He reviews other cases of giant calculi from the literature. Randall (1921) reported the largest one in both measurement and weight on record. The calculus weighed exactly 4 pounds (1.8 Kg.), with a longitudinal circumference of 48 cm. and a horizontal circumference of 40 cm. Anagnostidis (1937) reported a large vesical calculus; the measurements were 11 by 16 cm.; the weight was not given. Louca (1930) described a calculus that weighed 630 Gm., with a height of 9 cm., a length of 7 cm. and a circumference of 26 cm. Bride (1936) found a large vesical calculus, 112 Gm. in weight, with dimensions of 6.5 by 6.0 cm., which had occurred during pregnancy. Greenberg (1937) described a giant vesical calculus a little more than 1 pound (0.5 Kg.) in weight. Daland (1935) reported what probably is the second largest stone on record; he said that it was almost 2 pounds (0.9 Kg.) in weight.

In Crance's case, a man aged 74 years had a giant vesical calculus which was seen roentgenologically to fill the bony pelvis almost completely. With the patient under anesthesia induced by nitrogen monoxide and oxygen, a midline suprapubic incision was made, and the bladder was easily exposed without previous filling by catheter. The bladder was opened longitudinally for a distance of nearly 4 inches (10 cm.) because of the size of the stone. When the bladder was opened, a large white hard calculus was seen. An attempt was made to deliver the stone bimanually, but this procedure was quickly abandoned because of the trauma which possibly would result. Short obstetric

35. Crance, A. M.: Removal of a Giant Vesical Calculus with the Aid of Obstetrical Forceps, J. Urol. **45**:327-330 (March) 1941.

forceps were then applied in the customary manner, from above downward with the concave curve upward. Once the stone had been engaged in the forceps and clearly freed from the wall of the bladder, delivery was begun in an upward forward motion, and then by careful side to side movement the stone was delivered with only moderate difficulty and without additional traumatization of the original incision in the bladder. The stone was 1½ pounds (0.7 Kg.) in weight. Its perimeter was 35 by 29 cm.

Diverticulum.—Kimbrough [36] presents a study of the treatment of 30 patients suffering from diverticula of the bladder observed during a twelve year period. During this twelve year period 375 patients were treated by operative procedures for obstruction of the neck of the bladder. The incidence of diverticulosis was 8 per cent.

It is universally agreed that obstruction of the neck of the bladder, except for the rare congenital type, is essential to the formation of a diverticulum, the blowout effect described by Keyes. Hinman has advanced the idea that this reverse pressure may be supplied without definite changes in the neck of the bladder.

Prostatic hyperplasia with varying degrees of fibrosis and the formation of median bars accounted for obstruction in 22 cases in this series. Fibrosis of the neck of the bladder without apparent enlargement of the prostate was present in the remaining 8 cases.

Stricture of the urethra was a causative factor in 2 cases.

Twenty patients had single, and 10 had multiple, diverticula. In 3 cases the diverticula were situated at the fundus in the region of the attachment of the urachus; in 10, near the right ureteral orifice, and in 7, near the left ureteral orifice; in 9 cases the diverticula were multiple bilaterally.

The symptoms were those of prolonged obstruction at the neck of the bladder with the associated effects of infection. The intensity of the disturbance was in direct proportion to the extent and the severity of the cystitis.

The cystogram provides the most nearly accurate information concerning the size, the situation and the number of the diverticula.

In all cases of this series, a plan of treatment for the diverticulum was made and carried out prior to relief of the obstruction of the neck of the bladder. Six of the patients received no operative treatment for the removal of the sac.

Kimbrough believes that diverticula of a capacity greater than 50 cc. which do not empty on urination or those which carry troublesome infection should be removed. Capacity alone is not an indication for surgical

36. Kimbrough, J. C.: The Treatment of Bladder Diverticulum: Report of Thirty Cases, J. Urol. **45**:368-381 (March) 1941.

intervention. The amount of constriction at the neck and the severity of infection are important factors. In recent years, with the increase of standardization of transurethral resection for obstruction of the neck of the bladder, many diverticula have been left intact.

Kimbrough gives the general principles of the operative procedure: Adequate preparation should be carried out. Safe anesthesia should be employed, and if spinal anesthesia is used (which Kimbrough has found "the most satisfactory") not more than 100 mg. of procaine hydrochloride should be employed.

A midline suprapubic incision should be made with adequate mobilization of the bladder and without urinary contamination of adjacent tissues. Vasectomy prior to or at the time of the operation will prevent the annoying occurrence of epididymitis. Ureteral catheters should be inserted before an attempt is made to separate the sac. It is more satisfactory to carry out ureteral catheterization after the bladder is opened than to precede the operation with preliminary cystoscopy. The best method or combination of methods suitable for each case should be selected, the intravesical, the transvesical or the extravesical approach.

Adequate drainage of the extravesical space for five or six days is necessary except in the removal of small diverticula by the intravesical technic. Adequate closure of the wall of the bladder at the site of the excision of the sac should be done. Drainage after suprapubic cystostomy should be maintained until the obstruction of the vesical neck has been corrected.

An ample interval should be allowed between diverticulectomy and removal of the obstruction at the neck of the bladder. In Kimbrough's series the average time between operations was forty-seven days.

Fourteen of the 30 patients had prostatectomy performed for the relief of urinary obstruction. Thirteen of these were operated on by the suprapubic approach and 1 by the perineal approach.

Council [37] reports a new operative technic for the cure of diverticulum of the bladder. An inflated balloon inserted into the diverticulum and then distended serves as a guide and buffer, and the catheter serves as an excellent tractor. This method not only insures excellent exposure but also changes a difficult operation into a relatively simple one. Council is of the opinion that any diverticulum of the bladder can be removed by this simple procedure, provided the balloon fits the diverticulum snugly.

Ritter and Linder [38] discuss pseudopodial diverticula of the urinary bladder.

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37. Council, W. A.: A New Technic for Diverticulectomy of the Bladder: A Preliminary Report, J. Urol. **45**:382-387 (March) 1941.

38. Ritter, J. S., and Linder, H.: Pseudopodial Diverticula of the Urinary Bladder, Am. J. Surg. **49**:364-367 (Aug.) 1940.

They report a case in which the bladder of a man aged 64 years was found by cystographic study to be contracted in size and to have an hourglass constriction in its midportion. Five diverticula arose from the upper and four from the lower half of the bladder. Four of those arising from the upper half were small and resembled the ordinary type of diverticulum. The fifth one was a large piriform diverticulum arising from the right side of the upper half of the urinary bladder and extending down into the femoral region through the obturator foramen muscle for 3 inches (7.6 cm.). Three of the four diverticula arising from the lower half of the bladder extended down into the right femoral region and the midthigh. The fourth diverticulum extended down into the left femoral region and was divided into three parts by two constrictions. These diverticula ranged in shape from piriform to curvilinear sausage form to pseudopodial form and varied in size from 2 to 6 inches (5 to 15 cm.). Suprapubic cystotomy was performed, but the patient died a few days later. Permission for necropsy could not be obtained.

Periostitis.—Wheeler [39] reports 3 cases of what he believed to be acute Sudeck's atrophy of bone, not, as formerly called, periostitis pubis. He has been unable experimentally to produce periostitis of the pubis, although in a suprapubic operation he tried to include all the factors present in addition to injury of the periosteum. Because of the clinical picture and the roentgen observations, he believes this disease to have been acute atrophy of bone, a form of trophoneurosis. It is a self-limited disease which requires no surgical intervention.

PROSTATE GLAND

Surgical Procedures.—Dorman [40] states that prostatic resection is a satisfactory treatment for many types of obstruction of the prostate. In his series of cases, 84 per cent of all obstructing glands were treated by resection. Prostatic resection is the simplest and easiest way to relieve obstructive symptoms among more debilitated men and those suffering from advanced carcinoma. All urologists cannot become expert resectionists. However, urologists being trained at the present time should avail themselves of every opportunity to become proficient in the technic of resection. The importance of adequate equipment, of thorough preparation of each patient, of intelligent nursing care and of meticulous attention to the details of resection are stressed.

Livermore [41] states that dysuria, frequency of urination and nocturia may follow resection, just as they may follow prostatectomy.

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39. Wheeler, W. K.: Periostitis Pubes Following Suprapubic Cystostomy, J. Urol. **45**:467-475 (March) 1941.

40. Dorman, H. N.: Transurethral Prostatic Resection: A Statistical Study Based on Three Hundred Consecutive Cases, J. Urol. **45**:411-427 (March) 1941.

41. Livermore, G. R.: The Etiology of the Unsatisfactory Results Following Prostatic Resection, Tr. Am. A. Genito-Urin. Surgeons **33**:243-250, 1940.

Incontinence is a complication that can be prevented if the surgeon is careful never to cut proximally to the verumontanum. It may often be relieved by the application of fulguration in the internal meatus at the four points of the compass.

Late hemorrhage denotes malignant change or obstruction of the prostate gland.

Stricture is not caused by the coagulating or the cutting current. Stricture which follows resection is caused by passage of the large resectoscope without preceding this instrument with sounds gradually increasing in size.

Small tags and nodules which cause dysuria may be removed in the office with the resectoscope.

Resection in the hands of the best resectionists is still the operation of choice in all cases except those in which hypertrophy of the prostate gland is marked and extensive.

Creevy [42] reports the results of transurethral resection done for 1,141 consecutive patients. More than one operation was done for 23.9 per cent of the patients. The total mortality rate for the series was 4.4 per cent, and the average total hospital stay was 16.2 days. The average amount of tissue removed increased from 3.3 Gm. per patient in 1930 to 33.8 Gm. in 1940. The amount of tissue removed exceeded 30 Gm. in 21.9 per cent of operations in the whole series and in 38.3 per cent of those done in 1940, even though operations for contractures and small prostate glands, as well as all operations done by men just beginning to specialize in urologic surgery were included in the calculations.

The stay in the hospital in Creevy's cases was longer than that reported by many others; this was largely due to the fact that nearly all the patients were penniless and came from out of the city; thus they had to be kept in the hospital until they were ready to go to their homes. Then, too, these figures referred to total hospitalization and not merely to the postoperative stay.

For patients with impaired renal function, if fever was present or if complications required treatment, preliminary drainage was employed, including cystostomy for those whose recovery of function with the inlying catheter was poor, and in whom calculi were too large to admit of litholapaxy. On the other hand, patients who were in good condition and afebrile and whose renal function was normal had nothing to gain and everything to lose from preliminary drainage.

Spinal anesthesia was used for patients adjudged to be "good operative risks." Pentothal sodium was the agent employed for those with

42. Creevy, C. D.: Resection of the "Large" Prostate: Technique and Results, J. Urol. **45**:715-720 (May) 1941.

hypertension, cardiac disease or impairment of renal function and for those who manifested undue apprehension. These included about half the patients.

A tight meatus was never dilated but was always cut. Any dilatation present disappeared within a few minutes, and the tight meatus rode with the sheath, so to speak, alternately compressing and stretching the urethra, sometimes with disastrous results. If narrowing was present behind the meatus or if the prostate gland was high and anterior, perineal urethrotomy was done.

The mode of attack on the gland itself was that advocated by Nesbit. Resection was begun at 12 o'clock and was deepened until the circular fibers of the capsule were seen. This detached the lateral lobes from one another and allowed them to fall backward and medially. Resection was then carried down between the right lateral lobe and the surgical capsule, so that the circular fibers were exposed almost, but not quite, to the verumontanum, until the lateral and median lobes were attached by a rather slender verticle pedicle. The same operation was then done on the left. Bleeding was controlled, and the pedunculated lateral and median lobes were excised last. The left index finger was then inserted into the rectum to push remnants into the lumen for resection with one hand and to verify the completeness of the section by palpation.

The Foley bag was used routinely, but traction was employed only when bleeding was troublesome because of a conviction that traction promotes incontinence.

After operation, irrigation was carried out at frequent intervals with a closed sterile system consisting of a reservoir, rubber tubing, a glass Y tube, a clamp and a urine bottle. The rubber tubing was used for only 1 patient and was then discarded. The bag was usually removed in three days. If the surgeon felt that the operation had been incomplete, it was repeated before voiding was permitted. If urination was difficult or if there was any appreciable amount of residual urine, resection was repeated.

Lowsley and Kilgore [43] report a method of total perineal prostatectomy designed to give greater protection to the vesical orifice. This procedure has been used by them in about 20 selected cases with excellent results. It is not indicated in cases in which carcinoma of the prostate gland is known or suspected to be present.

An arcuate incision is made about 1 inch (2.5 cm.) above the mucocutaneous junction of the anus so that the subcutaneous fat and the central tendon are exposed. The central tendon is then carefully incised down to the wall of the rectum, a procedure which allows the transversus perinei muscles to be retracted anteriorly. The rectum is

43. Lowsley, O. S., and Kilgore, R. N.: Total Perineal Prostatectomy: A Modification of a Previously Published Technique, J. Urol. **45**:196-201 (Feb.) 1941.

dissected away from the overlying areolar tissue until the rectourethralis muscle is exposed. This muscle is then incised or retracted laterally; this allows the rectum to be dissected away from the base of the prostate gland. A transverse incision is then made in the fascia covering the vesicles; this permits greater mobility of the gland later in the procedure. Then a transverse incision is made through the urethra at the apex of the prostate gland; the straight prostatic tractor is passed through the prostatic urethra into the bladder and opened. When the tractor is depressed downward, the anterior commissure is exposed; this is separated from the overlying tissues by blunt or sharp dissection, thus bringing into view the anterior margin of the vesical orifice. The anterior commissure is divided in the midline so that the vesical orifice and the prostatic urethra are exposed.

A transverse incision is then made in the prostatic urethra, just distal to the internal sphincter muscle. If the intrusion of the lateral lobe is so marked that the internal sphincter muscle cannot be visualized, a midline incision may be made through the floor of the urethra so that the posterior and middle lobes of the gland are divided. This incision bisects the entire prostate gland up to the vesical orifice, and by the exertion of lateral traction on either half of the gland, good vision can be obtained. The prostate gland may then be freed from the floor of the vesical orifice on both sides under direct vision and with a minimum of trauma to the internal sphincter. Bisection of the prostate gland allows good exposure of the seminal vesicles, so that these may be removed easily or clamped and ligated with the vasa deferentia and the accompanying blood vessels. Bleeding vessels are easily clamped and ligated.

A catheter is then passed through the urethra and into the bladder. The vesical sphincter and the membranous urethra are approximated with interrupted chromic catgut sutures.

Dougherty [44] made an analysis of 87 cases in which death occurred after operation on the prostate gland. Heart failure, hemorrhage, and sepsis were listed as causes of death in 79.5 per cent of these cases.

The significance of a "bad cardiac history" was emphasized. Death from hemorrhage occurred only among those patients who had undergone transurethral and suprapubic operation. Since the increase in appreciation of the blood supply of the prostate gland and the development of the bag hemostat, the number of deaths from the hemorrhage among patients who undergo transurethral procedures has been negligible. Careful postoperative observation by the surgeon and by specially trained nurses and early steps directed toward control of bleeding are of supreme importance in the treatment of this complication.

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44. Dougherty, J. A.: An Analysis of Causes of Death in Prostatectomy, California & West. Med. **54**:216-218 (April) 1941.

For patients who have elevated leukocyte counts, even in the presence of normal temperature and heart rate, otherwise elective operations should be postponed until the results of blood counts are more nearly normal.

Urethral manipulation of the hemostatic bag or of catheters is to be avoided in the presence of fever. This disturbing complication is probably controlled best by drainage by catheter, rest in bed, forced administration of fluids and the use of urinary antiseptic agents.

When spinal anesthesia is used, an adequate dosage of procaine hydrochloride is suggested. Smaller doses may require reenforcement of anesthesia with ether, and this constitutes an added risk.

The preoperative making of pyelograms by the intravenous technic is advised as a means of increasing the sum total of knowledge of the patient's operability and probable postoperative course.

The chief factors in lowering the mortality rate for surgical procedures on the prostate gland are the instant recognition and the immediate treatment of complications.

Vest,[45] discussing the mortality rate accompanying surgical intervention on the prostate gland, gives the results of treatment in a consecutive series of 410 patients who were admitted to the public ward service of the Brady Urological Institute of the Johns Hopkins Hospital, Baltimore. Operative procedures for the relief of prostatic obstruction were carried out on 365 of these patients with only 6 deaths —a mortality rate of 1.6 per cent. All the patients were operated on by members of the resident staff who were receiving urologic and surgical training. The selection of the type of treatment, whether prostatectomy or transurethral resection, and the carrying-out of the necessary procedures and operations were entirely the responsibility of the residents. The condition of these patients on admission was similar to that of patients in other public ward services. Patients with prostatic obstruction were not refused admission to the hospital because of their condition or because they were likely to be "poor risks." The patients in this series were consecutive and included all who were admitted to the public wards during a five year period.

The low operative mortality rate is said to have been due to several factors: (1) proper preoperative care, including drainage by catheter for decreased renal function; (2) appropriate preoperative treatment of cardiac and other medical complications; (3) avoidance of suprapubic cystotomy except when absolutely necessary (this operation being done in only 5 per cent of the cases); (4) treatment by transurethral resection methods when the prostate gland consisted of small lateral or median

45. Vest, S. A.: Mortality in Surgery of the Prostate, J. Urol. **45**:439-450 (March) 1941.

bars, and (5) performance of prostatectomy when the gland was of moderate or large size.

Perineal prostatectomy is a safe and surgically sound method of treating moderately and extensively hypertrophied prostate glands. It gives excellent functional results, and there is less possibility of recurrence of the obstruction than there is after resection. In addition to the important fact that carcinoma can be recognized early and radically treated through the perineum is the fact that the perineal route affords dependent drainage to an infected bladder and lessens the chances for the development of serious infection of the upper part of the urinary tract.

It is only by the application of these principles and the selection of the proper type of operative procedure for each patient that a mortality rate of 1.6 per cent has been achieved in these cases, and in retrospect Vest thinks several of the 6 deaths that occurred probably could have been avoided. He points out that Young's report of 128, and later of 198, consecutive cases in which perineal prostatectomy had been done without a death concerned largely private patients. Commentators on Young's statistics have held that among patients in public wards the mortality rate is always high. Vest's report of a mortality of 1.6 per cent in 365 operations for the relief of prostatic obstruction among patients in public wards (the mortality rate for perineal prostatectomy alone being 1.2 per cent) shows that with proper care a low mortality rate can be obtained for patients in public wards, who usually enter the hospital in poor condition and with many complications.

Kackley [46] reports a total mortality rate of 2.4 per cent in a series of 290 cases in which prostatic obstruction was treated by transurethral resection with the galvanic cautery. Delayed hemorrhage was a factor in only 0.6 per cent of the cases. Immediate serious hemorrhage requiring cystotomy occurred twice (with 1 death).

An average of 18.5 Gm. of tissue was removed in each case. Eighty-eight per cent of the patients were free of residual urine within eight weeks, and 90 per cent were free within three months. Particular attention to thorough grooving of the lateral lobes of the gland and to leaving an adequate blood supply to all prostatic tissues is urged.

Davis and Nesbit [47] present comparative tabulated follow-up data on patients who underwent perineal prostatectomy and prostatic resection for benign prostatic hypertrophy. These data are based on an analysis of replies to questionnaires received at least a year after operation from

46. Kackley, E.: Galvanic Cautery Transurethral Resection: A Report of Two Hundred and Ninety Cases, J. Urol. **45**:451-466 (March) 1941.

47. Davis, E., and Nesbit, R. M.: Comparison of Late Functional Results in Perineal Prostatectomy and Transurethral Prostatic Resection, Tr. Am. A. Genito-Urin. Surgeons **33**:251-255, 1940.

100 consecutive patients who had been operated on by the one method and 100 who had been operated on by the other.

Although it is agreed by urologic surgeons that both prostatectomy and prostatic resection are major surgical procedures, the ordinary patient who is to undergo prostatectomy, influenced by his visible external incision, is inclined to view his operation more seriously than the patient who undergoes prostatic resection and will therefore more likely choose to remain in the hospital longer than is necessary. The average time required for the cessation of perineal urinary drainage after prostatectomy might serve as a fairer basis for comparison than the average period of postoperative hospitalization. The time required for closure of wounds averaged sixteen and a half days; the time of postoperative hospitalization averaged twenty-one days.

The hazard of postoperative urinary incontinence is to be reckoned with after removal of prostatic obstruction by any of the three recognized methods. Those with experience know that careful and honest analysis of any large series of cases of suprapubic prostatectomy will show that in a small percentage of the cases the operation was defective in this respect. Although no one denies the danger of damage to the external sphincter inherent in perineal prostatectomy, the occurrence of this complication after suprapubic prostatectomy indicates that unsatisfactory urinary control may occasionally result from weakness of the fibers of the external sphincter peculiar to the individual patient or that, possibly, it may result from a concomitant lesion of the central nervous system. Since this particular small follow-up series, consisting of only 100 cases in which replies were obtained, happens to include 2 cases in which real urinary incontinence was present (complete in 1 and partial in 1), the percentage of incontinence following perineal prostatectomy is more apparent than genuine.

Concerning prostatic surgical procedures, it may be said that in general cure may best be gaged by the postoperative frequency of urination by day and by night and, more particularly, by the patient's own satisfaction or disappointment with the degree of symptomatic relief obtained. Eighty-five per cent of these old men stated that they did not pass urine too frequently; 60 per cent reported that they urinated only once or not at all during the night, and 89 per cent voluntarily classified themselves as well.

Modern transurethral prostatectomy has been evolved during the past decade.

Low morbidity and mortality rates and excellent postoperative results can be obtained after resection if four cardinal principles are rigidly observed. They are: (1) avoidance of infection; (2) adequate control of hemorrhage during operation; (3) prevention of injury of the urethra, and (4) subtotal removal of the prostate gland.

The careful management of patients before, during and after operation by means of aseptic drainage systems has reduced sepsis to the status of an unusual complication.

A well planned and executed routine technic of operation enables the surgeon to control bleeding during operation in a completely efficient manner. The 100 cases of resection reported by Davis and Nesbit include only 1 in which postoperative hemostasis was required.

Subtotal removal of the prostate gland is essential to an uncomplicated postoperative course as well as to a satisfactory end result. It is felt that these can be attained most efficiently by the use of digital palpation during operation. Adequately performed transurethral resection should leave the capsule exposed throughout the prostatic fossa, and the urologist should employ resection only in those cases in which this type of removal can be attained. In other cases the patients should be treated by enucleation. In this series it was necessary to do secondary resection in 6 cases to complete the removal of tissue.

Four patients in this series had previously undergone resection, with imperfect results; Nesbit had operated on 3 of them. In each case an incomplete but seemingly satisfactory amount of tissue had been removed. All the glands were grade 3 in size, and 35, 60 and 52 Gm. of tissue had been removed, respectively, at the first operation. The patients were never entirely free from symptoms until after their return one, five, two and four years later, respectively. Secondary operation with complete removal of tissue yielded 69, 57 and 62 Gm. from 3 patients and had, at the time at which Davis and Nesbit wrote, apparently cured each patient. The fourth patient, a physician, had undergone resection three times previously in another clinic. Completion of prostatectomy for him required removal of 66 Gm. of tissue and resulted in normal urinary function.

It is the practice of Davis and Nesbit to perform open prostatectomy in those cases in which the prostate gland appears to be too large to resect in one operation of an hour's duration.

PENIS

Epithelioma.—In discussing epithelioma of the penis, Naegeli [48] states that all writers on the subject agree that balanitis or balanoposthitis is the most important single cause of carcinoma of the penis. All writers are in agreement that circumcision of all male infants is the one prophylactic measure of any value. Naegeli reports that Wolbarst reviewed the literature and circularized a number of large hospitals and cancer services. He was unable to find a single instance of the lesion in a Jew circumcised at birth, although he found one in an uncircumcised adult Jew.

48. Naegeli, F. D.: Epithelioma of the Penis, J. Urol. **45**:202-215 (Feb.) 1941.

Two types of squamous carcinoma of the penis usually are described, the papillary and the infiltrating type. Neoplasm of either type may arise from the mucous membrane of the glans penis or the prepuce; rarely does it spring from the skin of the shaft behind the corona or from the mucosa of the urethra. Most commonly, the neoplasm is papillary in type and originates on the glans. It starts typically as a small papillary or indurated nodule under a phimotic prepuce and enlarges at a rate proportional to the degree of its malignancy. Soon infection supervenes and a foul, sometimes bloody, discharge oozes from beneath the prepuce, which eventually may be perforated. Infiltration of the glans may result in obstruction to urination or to the formation of fistulas.

Metastasis probably takes place by embolism or by migration of a group of malignant cells whose travels terminate in the first lymph node encountered. Early removal of the primary lesion prevents embolic dissemination. The majority of patients suffering from carcinoma of the penis have palpably enlarged inguinal lymph nodes when they are first examined, but somewhat less than half of these nodes contain carcinoma cells. The enlargement in the rest is due to infection in the region drained by the tributary lymphatic vessels. Since it is frequently impossible to distinguish by palpation which glands are affected by metastasis, it may be desirable to defer dissection of the glands for a time after removal of the primary tumor to allow the adenitis to subside. Such a procedure may reduce the mortality rate of the combined one stage operation, particularly among patients whose general physical condition is poor.

There is no uniform sequence of the appearance of symptoms. Commonly, symptoms are not present until the primary lesion is extensive and metastasis is present. Drainage, or an increase in drainage, from beneath a phimotic prepuce may attract attention. Bleeding occurs in 10 to 20 per cent of the cases. Obstruction to urination and the formation of urinary fistulas are late developments. Enlargement of portions of the groins may occur at any time during the course of the disease, even before the primary lesion is noticed. The time elapsing between the appearance of the first symptoms and the visit of the patient for treatment in most instances averages from ten months to two and a half years.

All the forms of therapy for cancer have been applied to carcinoma of the penis, including the surgical, the electrosurgical, the radiotherapeutic and combinations of these.

Electrocoagulation of the primary lesion and electrodissection offer no advantages over surgical treatment. Fulguration frequently does not remove all the cancerous tissue, and it has been said that some tumors

are stimulated to more rapid growth after its use. Moreover, the penile scars which follow treatment by fulguration frequently are deforming and painful.

Radium is useful in carefully selected cases.

High voltage roentgen therapy has proved disappointingly ineffective against both primary and metastatic epithelioma of the penis, even when administered in fractional doses by the Coutard method.

The lesion rarely recurs in the penile stump, but it does recur in the groins. Evidence of its existence in the latter site usually appears within two years, although the literature directs attention to not a few instances in which it recurred four or five years after inguinal dissection. Occasionally, cure has resulted from secondary removal of the involved region. Roentgen and radium therapy have proved unsatisfactory for the control of recurrence.

Records of the 26 patients considered by Naegeli contain some mention of the presence or absence of phimosis. Phimosis was present in 20 instances; in 18 of these it was probably congenital. Six patients had been circumcised prior to admission; 4 from three months to three years after symptoms of cancer had developed; 1 twenty months, and 1 fourteen years, before cancer was noted.

URETHRA

Plastic Procedures.—In regard to extensive stricture of the urethra Dodson [49] states that it is well recognized that if a strip of mucosa can be preserved a satisfactory urethral channel will form about an indwelling catheter, provided healthy perineal tissue to be approximated over the catheter is present. When this treatment is not possible, most authors advise performance of perineal urethrostomy to create a permanent stoma.

When the perineal tissue overlying and supporting the urethra is injured or destroyed, the problem of successful repair of a urethral defect is much more difficult. Confronted with 2 patients who had such a condition, Dodson considered that the scrotum was the logical source from which to obtain tissue to aid in reconstruction of the urethral channel and to give the channel support and protection. The posterior portion of the scrotum can easily be shifted to the perineum. It has an abundant blood supply, which need not be interrupted, and the texture of the scrotal skin is but slightly different from that of the perineum.

In Dodson's first case a portion of the bulbous urethra was resected because of carcinoma. The local neoplasm was extensive and required excision of all neighboring perineal tissue except a portion of the skin.

49. Dodson, A. I.: Transplants from the Scrotum for the Repair of Urethral Defects, Tr. Am. A. Genito-Urin. Surgeons **33**:211-220, 1940.

The subcutaneous tissue of the scrotum was used to help bridge the gap in the urethra, to create an additional blood supply for the region and to furnish subcutaneous support.

The perineal urethra of Dodson's second patient was partly destroyed, and the overlying perineal tissue, including the skin, was entirely destroyed by periurethral phlegmon. A whole thickness graft from the scrotum was used for repair of the defect.

Davis [50] states that the Thiersch-Duplay method continues to be the foundation stone of the operative structure in the surgical treatment of hypospadias in men. It results in a hairless urethra of uniform caliber, and there is no limit to the length of the urethra which can be constructed. It is, however, difficult to carry a urethra that has been formed by the Thiersch-Duplay method fully to the end of the penis. For this reason and in view of the recent increased interest among plastic surgeons in pedicled tube grafts, Davis turned again to this oft-tried procedure.

A rectangular flap of skin is outlined on the dorsum of the penis. The pedicle is produced at the proximal end of this flap, and at this end its edges are made to diverge so that the new meatus will be sufficiently large and any tendency to contracture will be avoided. The sutures used are interrupted and are of the finest plain catgut (at first no. 000; later, no. 0000).

With this arrangement it was soon found that the blood supply was much better than it was when the flap was left attached by its distal end. Consequently, the tube graft could be made as long as the length of the penile skin allowed, without sloughing. The proximal attachment also allowed the penis to be bent over dorsally, so that the entire length of the tube graft could be utilized. The procedure finally evolved was to measure the length of the tube graft and then to measure an equal distance on the central surface of the penis, beginning at the tip of the glans. Over this distance a tunnel was produced by means of a sharp-pointed bistoury, and it was enlarged by means of a grooved director and scalpel to such a size that the tube graft could easily be drawn through it. The tube graft was fastened in place by four sutures which joined its extremity to the adjacent skin, and by three sutures at the new meatus, all of no. 000 plain catgut. In some cases, a single additional suture of fine black silk was placed at the meatus.

The results of this procedure show that the grafts survived perfectly in all of 6 cases.

After the lapse of two or three weeks, the pedicle is divided, so that the meatus is left situated at the tip of the glans in its normal and proper position.

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50. Davis, D. M.: The Pedicle Tube Graft in the Surgical Treatment of Hypospadias in the Male and a New Method of Closing Small Urethral Fistulas, Tr. Am. A. Genito-Urin. Surgeons **33**:221-235, 1940.

The new glandular urethra may be joined to the original urethra by a Thiersch-Duplay plastic procedure during the same operation, or if there is any reason for delay, the joining may be done later. The covering-in phase of the Thiersch-Duplay plastic procedure, to complete the new urethra, has always been a difficult part of the technic. If penile skin is used, it must be brought together under considerable tension, and in addition the suture line in the skin lies directly or almost directly over the suture line in the new urethra, so that the development of persistent fistulas is practically inevitable. This may be avoided if the anterior surface of the scrotum is incised and the penis is sutured down to the scrotum.

The small fistulas which frequently remain after construction of a new urethra constitute perhaps the most annoying and discouraging feature of surgical operation for hypospadias. The method Dodson has evolved for closing them has succeeded on every 1 of 4 consecutive occasions, an impressive record. After the fistula is cut around and the skin is undermined in the usual way, a straight needle threaded with silk thread is inserted eye first in the new meatus and is brought out through the fistula. The cut outer edges of the fistula are caught with the silk thread, and the other end of the thread is passed out again through the meatus. The result is that when the two ends of the thread are pulled the fistula is turned completely inside out and made to project into the lumen of the urethra. This inversion of the fistula is maintained by fastening the thread to the abdominal skin through an intermediary rubber band. The silk thread pulls out within from two to four days, but by this time healing is almost complete.

The methods described by Davis have been used for 6 other patients who were in various stages of treatment at the time of his report. These methods have been beneficial and lend a new note of confidence to operative plans and procedures. Davis adds a note of warning, however, stating that the surgical treatment of hypospadias is a fascinating procedure for those willing to devote the time and effort necessary to become competent in it but that it should not be attempted by any others, since neither the surgeon nor the patient is likely to benefit from inexperience or lack of careful attention and application to the exacting technic required.

Nesbit [51] states that operations for the correction of hypospadias in men are designed to fulfil two purposes: (1) correction of ventral deformity and (2) construction of a penile urethra.

The ideal attainment of these two objectives should provide an end result in which the phallus is free from ventral scar, so that normal

51. Nesbit, R. M.: Plastic Procedure for Correction of Hypospadias, Tr. Am. A. Genito-Urin. Surgeons **33**:237-239, 1940.

sexual function is possible, and in which the urethra is of adequate caliber and is entirely free from growth of hair.

Nesbit believes that the procedure with which his report is concerned allows attainment of these objectives. It provides for correction of deformity at the first stage without any midline scar and leaves the ventral surface covered with normal skin which bears no hair and subcutaneous tissues which are freely movable on the subjacent penile structures and are thus suited for the Thiersch, the Duplay or the McIndoe type of urethroplasty.

Circumcision is carried out 0.5 cm. from the corona. Subcutaneous dissection denudes the phallus easily except at the midline on the ventral surface, where there are situated the fibrous remains of structures embryologically designed to cover the corpus spongiosum. These fibrous elements are completely removed by sharp dissection, so that straightening of the penile shaft with a relatively proximal displacement of the urinary meatus is allowed. A buttonhole incision is now made in the dorsal skin flap at a suitable point, and the glans penis is brought out through it. A line of interrupted silk sutures fixes the free edges of the buttonhole incision to the skin adjacent to the corona. The skin flap distal to the buttonhole incision now folds downward to cover the ventral defect, and final closure is made by a transverse suture line.

Experience with a number of patients who have undergone this first stage procedure has demonstrated its value. Such patients have obtained complete correction of deformity, and the skin graft which has been transplanted from the dorsal to the ventral surface has been devoid of scar. It moves freely on subjacent structures.

Urethroplasty by means of the technic of Thiersch or of Duplay is performed easily and advantageously at the second stage. The fact that the skin and subcutaneous structures are normal facilitates the handling of them, and the increased circumference of the penile integument which results from the first stage procedure helps materially to prevent the exertion of any tension on suture lines on closure of the outer edges of the skin. Further, the urethra is lined by skin which is not hair bearing.

Nesbit prefers the Duplay type of urethroplasty, in which stainless steel subcuticular sutures are utilized for closure. With this technic, only two sutures are needed for the entire urethroplasty: one for closure of the urethral skin tube; the other for closure of the outside skin wound. These stainless steel sutures cause a minimum of reaction and infection and are easily removed on the fourteenth postoperative day.

Diverticulum.—Parmenter [52] discusses diverticulum of the urethra in women and reports 8 additional cases.

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52. Parmenter, F. J.: Diverticulum of the Female Urethra, J. Urol. **45**:479-496 (March) 1941.

There is no general agreement on the question whether the origin of the diverticulum is congenital or acquired. Probably both views are correct.

A diverticulum of the urethra may cause frequency, urgency and difficulty of micturition, a lump in the vagina, pain on walking or during coitus, or an intermittent discharge from the urethra.

The diverticulum, which feels soft and fluctuating, can be easily recognized on vaginal palpation. If pressure is exerted on it with the labia separated, pus, urine or both will be seen to drip from the meatus with disappearance of the mass. Cystourethroscopy will demonstrate one or more openings, usually situated on the floor of the urethra or slightly above on the lateral walls. The opening of the diverticulum usually is situated just in front of the sphincter muscle. A small ureteral catheter can be passed and will coil up in the diverticulum and be readily shown in a roentgenogram. The important point in diagnosis is careful palpation of the urethra through the vagina. The diverticulum, even if small, can be easily identified. It is necessary to separate the labia so that the expressed secretion may be seen as it leaves the meatus.

Successful treatment may be conservative or radical, although the latter undoubtedly is the method of choice except under exceptional circumstances. The technic used is radical removal of the sac, which is ligated and amputated at the urethral junction. The stump is inverted up into the urethra by two layers of interrupted no. 00 chromic gut sutures. The mucous membrane is closed with no. 1 chromic gut suture. Silk is not used, because it may play the part of a foreign body, as it did in one of Parmenter's cases of vesicovaginal fistula. An indwelling catheter, which must be kept draining, is left in place for ten days. The vagina is also lightly packed with gauze soaked in an approved antiseptic agent, and the gauze should be changed either daily or every other day, as indicated. Use of one of the ordinary urinary antiseptic agents, which has been utilized internally a few days prior to operation, is continued.

Engel [53] calls attention to urethral diverticulum in women, a lesion which he believes is commonly overlooked.

The bulk of evidence favors the theory of acquired origin of this condition, and he believes that the lesion arises from infected periurethral glands which, in reality, form periurethral cysts which later rupture into the urethra.

There are no characteristic symptoms, but a urethral diverticulum should be suspected in any patient with a history of swelling in the anterior wall of the vagina or about the urethra. Any woman with recurrent or persistent vesical symptoms should be asked about this item when the history is being obtained.

53. Engel, W. J.: Diverticulum of the Female Urethra, J. Urol. **45**:703-709 (May) 1941.

The treatment of choice is surgical removal; it was carried out in 4 of Engel's 5 cases with completely satisfactory results.

TESTIS

Tumor.—Huffman [54] reports a case of unusual testicular tumor which presumably originated from the interstitial cells, and discusses the subject of interstitial cell testicular tumor. Including Huffman's case, there have been reported 13 cases of tumor of this type. In 6 cases the tumor was on the left side; in 5 it was on the right; in 1 it was bilateral, and the side affected in 1 case is not known. In 5 of these cases the condition appeared in childhood, and in 4 of these precocious puberty occurred. In 2 of these 4 cases regression of the secondary sexual changes occurred after orchidectomy. Huffman's case is the only instance in which the condition of gynecomastia occurred during the childhood of the patient. In 2 adult persons gynecomastia occurred, but regression ensued after orchidectomy.

Ormond and Prince [55] review cases of malignant tumor of the testis in which the patients were seen at the Henry Ford Hospital, Detroit, during the twenty-six years prior to their report; they discuss some points of special interest.

The most common symptoms are swelling and pain, but swelling is observed twice as often as pain. Other symptoms reported are abdominal tumor and loss of weight.

During the quiescent period of growth, the neoplasm is limited by the resistance of the tunica albuginea testis and for a long time retains the shape of an enlarged testis. The shape is typically oval, although spherical tumors are sometimes encountered. The consistency varies greatly. The smaller, slowly growing teratomas may be of uniform stony hardness, but the larger tumors, which contain portions of cartilage, cystic portions and portions of soft vascular carcinoma are of course irregular. Almost all tumors in the series reviewed by Ormond and Prince were smooth, and none were large.

Hydrocele is said to accompany testicular tumor in from 15 to 25 per cent of the cases, and it may be necessary to aspirate the fluid from the hydrocele before the testis can be palpated accurately.

Metastasis from tumor of the testis occurs chiefly by way of the normal lymphatic drainage of the testis, that is, along the spermatic artery to the retroperitoneal lymph nodes. Then the spermatic, epigastric, mediastinal and supraclavicular glands may become affected.

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54. Huffman, L. J.: Interstitial Cell Tumor of the Testicle: Report of a Case, J. Urol. **45**:692-698 (May) 1941.

55. Ormond, J. K., and Prince, C. L.: Malignant Tumors of the Testicle, J. Urol. **45**:685-691 (May) 1941.

Trauma has often been credited with inciting the growth of tumor in the testis, but it seems rather well agreed now that one physical insult could hardly cause malignant degeneration, especially in view of the fact that the trauma to which it is attributed is often of a relatively unimportant nature and in view of the vast number of similar instances of trauma which are not followed by the formation of tumor. Trauma to the testes is common, and it is easy to attribute increase in the size of a tumor to a previous episode of trauma. However, it is possible that trauma may excite rapid growth in a small preexisting tumor or that it may serve to call attention to a neoplasm hitherto unnoticed. The series of Ormond and Prince is somewhat unusual in that trauma was mentioned as a possible cause of the lesion in only 4 instances.

The relation of cryptorchidism to tumor has aroused much discussion. The question is not yet settled, but it seems probable that cryptorchidism is a factor of importance, and this probably constitutes an added reason for the performance of orchidopexy. Of the 21 patients included in this report, 1 was a cryptorchid.

There are two chief forms of tumor which affect the testis: the homogeneous tumor, composed of cells of a single type, and the mixed tumor, or teratoma.

There are at present five methods of treatment: (1) orchidectomy alone; (2) roentgen therapy alone; (3) orchidectomy followed by roentgen therapy; (4) orchidectomy with preoperative and postoperative roentgen therapy, and (5) radical orchidectomy with removal of the draining lymphatic vessels.

Orchidectomy alone is now rarely practiced, and in most series of such cases in the literature dismal results are reported. However, Rees treated 38 patients by orchidectomy alone and obtained a four year survival rate of 13.2 per cent.

The method advocated by most urologic surgeons is orchidectomy followed or both preceded and followed by roentgen therapy, and these two modifications of the operation seem to have about an equal number of adherents. Ormond and Prince report that Dean and Barringer of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, are the chief proponents of both preoperative and postoperative roentgen therapy and that their results are extremely good. Whether the results would have been any worse if the preoperative treatment had been omitted may be questioned.

The Mayo Clinic reported long survival obtained by repeated courses of roentgen treatment in patients who had massive metastasis.

The radical operation is used by few. The mortality rate for this operation is high. Moreover, considered theoretically, on the basis of the anatomy of the lymph vessels, the radical operation seems to be

contraindicated, for the drainage from the testes frequently is to the lymphatic vessels on both sides of the aorta, and crossed metastasis has been observed.

Of those patients in whom metastasis was not demonstrable at the time of operation, only 2 were known to be dead at the time Ormond and Prince made their report; 5 patients, or 50 per cent, lived for more than five years; 7 patients, or 70 per cent, lived for more than four years. Moreover, the ones who received roentgen therapy were living, and the 2 who died had received none.

Of those patients in whom metastasis was demonstrable at the time of operation, all who had been traced were dead, except 1 who had lived five months after operation at the time of the report. None lived more than two years, and most died within a year. In view of the results obtained by others, this would indicate that the patients with metastasis probably received an inadequate amount of roentgen treatment.

Two conclusions seem to be inescapable: (1) that the presence or absence of demonstrable metastasis is of great prognostic significance and (2) that adequate roentgen therapy is of great importance.

Barringer and Earl [56] report the results of a survey of 37 cases of teratoma testis in which necropsy was done. The ages of the patients ranged from birth (1 stillborn child) to 47 years.

Records such as these have clarified many points as to the path of metastasis and the reasons for the inadequacy of radiation therapy for many of these patients. Metastasis may be, and generally is, both lymph borne and blood borne. If a left supraclavicular signal node is present, there is probably a chain of nodes with metastatic involvement along the course of the thoracic duct.

The lungs were involved in 78 per cent of the cases. The liver was involved in 75 per cent of the cases in which there was pulmonary involvement. The genitourinary tract was involved in 24 per cent of all the cases. The mediastinal nodes were involved in 55 per cent of the cases in which there was pulmonary metastasis. In 72 per cent of all the cases there was bilateral involvement of the abdomen, either of the lymphatic glands or of the intra-abdominal organs, such as the liver, the kidneys or the spleen.

Randall and Chamberlain,[57] in discussing the results of the treatment of testicular tumors for which preoperative roentgen therapy was carried out, state that they observed 17 patients for whom the prognosis was hopeless because of metastasis. Many died soon after the beginning

56. Barringer, B. S., and Earl, D.: Survey of Thirty-Seven Autopsied Cases of Teratoma Testis, Tr. Am. A. Genito-Urin. Surgeons **33**:269-295, 1940.

57. Randall, A., and Chamberlain, G. W.: Results of Treatment of Testicular Tumors: Analysis of the Advantage of Pre-Operative Roentgen Therapy, Tr. Am. A. Genito-Urin. Surgeons **33**:297-299, 1940.

or during the course of irradiation of their tumors. None of those with metastasis that extended above the diaphragm lived. Judged in the light of recent observations, only 8 of the 17 patients received adequate treatment. Of these 8, 3 were still living and well at the time of the report, three, eight and a half and eleven years, respectively, after removal of the primary tumor. These cases and many others reported in the literature conclusively demonstrate the value of radiation therapy in the treatment of a malignant growth of the testicle. Opinions differ, however, as to when such therapy should be instituted.

In 1932 Randall and Pancoast advocated and began the preoperative irradiation of tumor of the testis. The distal portions were treated first, and the testicular tumor was irradiated only after treatment had been administered to the lymphatic vessels draining the testes. The blood counts were watched, and the tumor was removed four to six weeks after treatment. Twelve patients were treated by this method. Eleven were living and well at the time of the report.

Ninety-one per cent of the 45 patients whose tumors were irradiated before operation were living and well two or more years after treatment. Fifty-six per cent of those who had been operated on and had then received radiation therapy before there was clinical evidence of metastasis were living and well two or more years after treatment, and 17 per cent of those who received delayed radiation treatment were living at the time of the report.

On the basis of this study, Randall and Chamberlain recommend the following procedures for the treatment of malignant tumor of the testis: (1) prompt diagnosis by means of the history, the results of physical examination and the results of studies of the urine for gonadotropic content of excretory urograms for the detection of abdominal tumors, as well as of roentgenograms of the involved testis and the thorax; (2) preoperative irradiation of the region of primary and secondary lymphatic drainage of the testis, and then of the tumor itself, and (3) orchidectomy within approximately four weeks.

Cahill [58] discusses testicular tumor and reports on the radical operation for this condition. This operation for tumor of the testis seems to occupy an uncertain position among urologic procedures. The concentration of tumor therapy as a whole in the hands of those who employ radiation and the radiosensitivity of certain of the testicular tumors have resulted in the presentation of well tabulated studies on such tumors and the effect of radiation on them, with or without castration.

The radical operation seems to have had the benefits of no such studies. Hinman, however, reported on the frequency of performance of the operation. Thirty-five surgeons reported to him by letter that

58. Cahill, G. F.: Testicular Tumors: A Report upon the Radical Operation. Tr. Am. A. Genito-Urin. Surgeons **33**:301-309, 1940.

they had done the operation in 91 cases. To these 91 cases he added 9 of his own, bringing the total to 100 cases in which the operation had been performed. Up to the time of Cahill's report, a relatively small number of urologic surgeons had given the procedure more than a casual trial. Ten surgeons had done 63 of the 100 operations. Of particular interest in Cahill's report is the fact that 20 patients, or a fifth of all the patients operated on, had lymphatic metastases impossible to remove, so that the planned procedure could not be carried out. The attempts at surgical removal of widespread metastases of tumors situated elsewhere have not been productive of good results, so that no better results may be expected from such removal of metastases of testicular tumors.

After several attempts to remove metastases which could not be separated from essential vessels, a study was made of those cases in which the patients afterward were submitted to the radical procedure, to ascertain, if possible, whether or not metastases were demonstrable. A supraclavicular metastasis is palpable; an intrathoracic metastasis can be shown by roentgenograms if it is in the pulmonary tissues; it is also demonstrable if it is in the mediastinum. An extensive epigastric or retroperitoneal metastasis is palpable. The usual metastatic pathway from the testis is in the same fascial planes as the ureter and crosses the same lymphatic vessels. It may and does involve the lymphatic vessels near the hilus of the kidney and the edge of the psoas muscle or the preaortic group. Some of these planes and tissues may be outlined roentgenographically. Cahill endeavored to determine by roentgen examination whether there were changes in the edges of the psoas muscles or in muscle shadows and by intravenous urography and retrograde pyelography whether there were extrinsic apparent deflections of the ureter or the pelvis. In cases in which the metastatic involvement is extensive, such changes are marked. This was shown in 2 cases; in both there was extensive involvement by a tumor secondary to the one in the testis. Involvement of the kidney or the ureter itself may occur, as was demonstrated in a case in which a metastatic mass secondary to a testicular tumor involved the ureteropelvic junction, causing hydronephrosis. When such obvious extension is present, radical surgical treatment is not feasible.

Cahill cites 55 cases of testicular tumor recorded in the J. Bentley Squier Urological Clinic, New York. Those in which the patients were treated directly by the radiotherapy department were not included. Eighteen patients were selected for radical operation. For 17 of these primary complete operations had been attempted, and for 1 a secondary radical operation had been tried. In 3 of the operations done between 1928 and 1932 irremovable metastatic processes had been encountered. In this same period the 1 secondary radical operation (removal) just mentioned had been attempted. Since 1932 all the patients selected for

the operation were patients concerning whom no criteria could be developed that would show extension of the tumor previous to operation. In all these patients the operation was completed primarily. In 5 of the 14 cases in which the operations were completed, tumor cells were demonstrated microscopically somewhere in the lymph nodes or vessels in the removed tissue.

Three patients who had been operated on before 1932 died of the disease; in all these the operation had been incomplete because of metastasis which should have been demonstrated previously. All had tumor masses which involved the preaortic vessels. With subsequent experience these patients would not have been selected for the procedure.

When this particular operation was considered in the light of those cases in which it was completed, Cahill found himself in accord with Hinman as to its feasibility and as to the ease of dissection of the primary preaortic lymph zone from the testis. There were no complications or operative deaths in Cahill's 18 cases. The healing of the larger incisions was uniformly rapid, and there was at the time of writing no weakness or hernia in any of the cicatrices.

A comparison of the results obtained by this operation with the results obtained in the 37 cases in which irradiation of the tumor was practiced with or without castration showed, at the time of the report, 17 of the 37 patients dead of the disease in contrast with 3 of the 18 patients for whom radical operations had been attempted or completed.

Randall,[59] in discussing the treatment of patients with testicular tumor, states that it is a rare privilege to be able to look back over the short period of ten years and see a definite radical change in the whole procedure of helping these patients to become well again. He calls attention to Tanner's report dealing with 425 cases of orchidectomy alone; the results presented four years after operation showed that only 5.3 per cent of the patients were cured. If Tanner had said that the mortality rate was 94.7 per cent, Randall says, he would thereby have emphasized the acute need of a change in the therapeutic program for such patients. Tanner's report was followed by that of Wasterlain, who recorded a "cure" rate of 6 per cent, so that again a mortality rate of approximately 94 per cent obtained.

It was then that Hinman brought out his radical operation. In his first report it was seen that the average rate of cure had increased to 17 per cent or, conversely, that the rate of failure had receded to 83 per cent.

Hinman concluded his remarks with a succinct sentence: "Orchidectomy, even with early diagnosis, is a dismal failure." This was aug-

59. Randall, A., in discussion on papers of Barringer and Earl,[56] Randall and Chamberlain[57] and Cahill,[58] Tr. Am. A. Genito-Urin. Surgeons **33**:310-314, 1940.

mented later by a remark Keyes made, namely that in the treatment of tumors of the testis "without irradiation prognosis is utterly bad." For twelve years Randall and Chamberlain have been attempting to change this picture. Their material has not been nearly so great as that indicated by the figures which come from the Memorial Hospital and from Hinman's clinic, but they are happy to be able to report a cure rate of 91 per cent and a mortality rate of only 9 per cent. Thus, within ten years there has been a complete reversal of the picture in the matter of this particular disease.

A number of urologists emphasize one criticism of preoperative irradiation of the tumor, that by this means lesions are destroyed, so that the histologist is not able to state definitely the type of tumor which has been destroyed. This may be said to be the pathologic point of view. Consideration of the patient should and does come first. Randall and Chamberlain know of 1 interesting case in which because of an error in the technic of irradiation a gap of about 1 cm. occurred between the lead screen and the limit of the application of the roentgen rays over the region of the right groin. This case was interesting in that it was proved by surgical removal that the tumor was situated in precisely the portion of the tissue affected by the gap in the screen.

Chamberlain presents (and Cahill has had similar experiences) 3 or 4 cases in which abdominal metastasis pushed the kidney out of place, rendering it nonfunctioning (by displacement or pressure on blood vessels or ureteral occlusion) but in which the kidney regained normal function (bilaterally) after radiation removed the abdominal metastatic process. Such cases, first, constitute evidence of what renal function can and will do, and, second, impressively show the effect of radiation on such metastatic neoplasms.

Other considerations that should be accentuated are, first, essential irradiation of the supraclavicular region and the starting of irradiation from the periphery toward the primary tumor, and, second, deferment of diagnostic study of such a patient until a urogram has been made according to the intravenous technic.

Barringer,[60] in discussing testicular tumors, congratulates Chamberlain on his excellent results in the matter of recovery, a rate of 91 per cent in cases in which the opportunities were most favorable. He commends Cahill for his extraordinary percentage of operative cures. He was inclined to believe that such figures as Randall and Chamberlain presented will be lessened as more cases are recorded.

Barringer mentions irradiation of one testis and the possibility of inflicting damage on the other by this procedure. This is a most

60. Barringer, B. S., in discussion on papers of Barringer and Earl,[56] Randall and Chamberlain[57] and Cahill,[58] Tr. Am. A. Genito-Urin. Surgeons **33**:310-314, 1940.

important point in the minds of all patients. He thinks that some damage is inflicted on the other testis (the uninvolved one) no matter how carefully it is screened. Lead screens may be placed around it, but no matter what is done, it receives radiation to some extent. The spermatogenic function as evidenced by the presence of viable spermatozoa disappears within six months. In some cases this function may reappear about two and a half years later.

Barringer draws attention also to 5 of Cahill's cases. In all cases the tumor was seminoma, which is notably radiosensitive. Barringer says that he would rather undergo irradiation of such a tumor than the operation. Yet he thinks it questionable that radiation will control a radiosensitive tumor with small metastases.

UROGRAPHY

Smith and Leadbetter,[61] in discussing intravenous urography, state that the data obtained from a series of persons with severely damaged kidneys were analyzed in an attempt to learn which tests of renal function will reveal whether intravenous urography may be expected to give satisfactory results. They found 2 instances in which satisfactory pyelograms had been made of kidneys that were unable to concentrate to a specific gravity of more than 1.008 or 1.009. Adequate excretion of the medium may be obtained when the concentration of nonprotein nitrogen in the blood is as high as 50 mg. per hundred cubic centimeters.

The most constant indication of the inability of the kidneys to excrete urographic mediums in concentrations sufficient to cast a shadow has been a low excretion of phthalein. Kidneys with a phthalein output which is less than one third normal are unlikely to give satisfactory results with intravenous urography.

Bourne and Hefke [62] state that the intravenous technic of urography for infants and young children has not been altogether satisfactory. In many instances shadows cast by intestinal gas obscure the urogram to the point of unreadability.

Even careful preparation by the administration of laxative agents, enemas and pitressin does not improve the diagnostic results in pyelography for such patients. Much of the gas in the intestinal tract is caused by air which is swallowed when the child cries and sobs during the procedure.

According to Bourne and Hefke, tomography offers a new method for improvement of intravenous pyelography for infants and young children. This procedure allows the reproduction of certain layers of the body, with elimination of shadows of other layers which may lie

61. Smith, G. G., and Leadbetter, W. F.: A Note on the Limitations of Intravenous Urography, Tr. Am. A. Genito-Urin. Surgeons **33**:137-143, 1940.

62. Bourne, N. W., and Hefke, H. W.: Body Section Pyelograms in Children, J. Urol. **45**:296-302 (March) 1941.

either above or below the desired level. This is done by blurring the otherwise clearly defined layers. The x-ray tube and the film carrier (Bucky tray) are moved in coordinated opposite directions by a two-armed pendulum which moves with an adjustable axis. The upper arm carries the tube, and the lower arm carries the film tray. At the level of the fulcrum all objects are clearly defined in a layer which is about 1 cm. wide. The method produces a roentgen demonstration of a layer of the body which traverses the renal pelves, calices and ureters. The interfering gas shadows are blurred and do not obscure the pyelographic details. In most cases in which unsatisfactory pyelograms would result from the intravenous technic, good diagnostic roentgenograms can be produced by the simple procedure of tomography.

HYPERTENSION

Nesbit and Ratliff [63] state that experimental evidence and clinical observations have shown that hypertension may result from pathologic conditions of the kidney; these may be bilateral or unilateral.

Three different types of unilateral renal lesions are most commonly associated with hypertension: (1) those produced by gross occlusion of the renal arteries, including trauma to the kidney; (2) the obstructive uropathologic conditions, and (3) chronic inflammatory lesions.

Since chronic infection appears to be the most important single causative factor, it seems that the best treatment of this type of hypertension is prophylaxis. In this regard the value of modern chemotherapeutic methods for prevention of chronic infections of the urinary tract cannot be overemphasized.

Nesbit and Ratliff believe that hypertensive patients should be submitted to complete urologic study as a part of the routine examination, even in the absence of a history of renal conditions or of urinary observations suggestive of disease of the urinary tract.

The rational treatment of the hypertensive patient suffering from unilateral nephropathy is removal of the diseased kidney, provided that the function of the opposite kidney is not importantly reduced. If this restriction is borne in mind a reasonable expectancy of improvement or cure can be had in the majority of cases.

Wear and Jacobsen [64] state that secondary hypertension occurs among approximately a third of the patients with prostatic obstruction. More than 50 per cent will report some evidence of unstabilized blood pressure. Residual urine in the bladder is not the sole factor in the elevation of intrapelvic pressure. Pyelectasis and ureterectasis are the

63. Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Renal Disease, J. A. M. A. **116**:194-199 (Jan. 18) 1941.

64. Wear, J. B., and Jacobsen, R. W.: Observations on the Incidence and Etiology of Hypertension in Prostatic Obstruction, Tr. Am. A. Genito-Urin. Surgeons **33**:73-76, 1940.

results of increased pressure within the urinary tract and do not constitute an index of hypertension. Increased intra-abdominal pressure results each time the patient attempts to void. Increased intra-abdominal pressure may elevate blood pressure by acting directly on the abdominal vessels or by increasing intraureteral and intravesicular pressures.

SULFANILAMIDE THERAPY

Deming, Sadusk and Wilson [65] state that the administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), whether in an acid or an alkaline medium, may be fraught with serious renal or ureteral complications.

Daily studies of the blood and the urine should be made for the free, the total and the acetylated form of sulfapyridine.

It seems unwise to administer this drug in the presence of obstructive pathologic changes in the urinary system.

The concretions of acetylated sulfapyridine are nonopaque to roentgen rays, but this fact should in no way influence the diagnosis.

There is a likely possibility that such concretions may serve as a nidus for further deposition of urinary salts with the later formation of stones.

Should anuria develop, recanalization of the obstructed ureters with lavage of the renal pelvis should be instituted at once, because anuria has resulted in several deaths, which have been reported in the literature. Recanalization should be attempted in the face of even the most serious complications. Successful results were obtained for 2 seriously ill patients with this procedure.

Sudusk, Waters and Wilson [66] report 2 cases in which complete anuria occurred during sulfapyridine therapy. In both cases anuria was caused by calculi blocking the urinary tract at the ureterovesical orifices. Treatment by means of cystoscopy was successful. The pathologic changes in the upper portion of the urinary tract of a patient who died of a neurosurgical complication consisted essentially of great tubular and capsular dilatation, marked congestion and vacuolation within the glomerular tufts and acute hemorrhagic pyeloureteritis, which extended into the adjacent renal medullary tissue.

Emmett and Hammer [67] present a study of the prophylactic use of sulfanilamide for the control of postoperative infection of the urinary

65. Deming, C. L.; Sadusk, J. F., Jr., and Wilson, D. E.: Sulfapyridine Anuria, Tr. Am. A. Genito-Urin. Surgeons **33**:127-135, 1940.

66. Sadusk, J. F., Jr.; Waters, L., and Wilson, D.: The Treatment of Anuria Due to Sulfapyridine Calculi, J. A. M. A. **115**:1968-1973 (Dec. 7) 1940.

67. Emmett, J. L., and Hammer, H. J.: Prophylactic Use of Sulfanilamide to Control Postoperative Infection of the Urinary Tract, Proc. Staff Meet., Mayo Clin. **15**:801-806 (Dec. 18) 1940.

tract. The patients followed were women who had undergone gynecologic operations and who had been treated for postoperative retention of urine either by intermittent catheterization or by the insertion of a retention catheter.

The routine procedure adopted was administration of 200 cc. of an 0.8 per cent solution of sulfanilamide (25 grains, or 1.6 Gm.) subcutaneously on the day of the operation; this was repeated daily until the patient could tolerate tablets taken by mouth. Administration of the drug was then stopped, and the patient received 5 grains (0.3 Gm.) of sulfanilamide three times a day. If catheterization had not become necessary by the end of the fourth postoperative day, the administration of sulfanilamide was discontinued. If catheterization was necessary or if a retention catheter was in place, administration of the drug was continued until the patient left the hospital (which in most cases was on the twelfth or fourteenth day after operation). After the patient had been dismissed from the hospital, the specimen of urine that had been obtained by catheterization was centrifuged and a wet smear prepared with Gram's stain and examined microscopically. In most cases cultures were made.

Emmett and Hammer's report is based on the study of 197 patients. The efficacy of treatment was judged by the amount of pus found by microscopic examination of the wet smear of a centrifuged specimen of urine obtained by catheter.

The results of prophylactic treatment in the 197 cases were as follows: The incidence of infection of the urinary tract was only 18 per cent; there was an incidence of 50 per cent in the control group. Of the group of 197 patients, 115 required the use of a retention catheter. The results of the prophylactic treatment of these patients showed an incidence of infection of the urinary tract of 25 per cent; there was an incidence of 72.5 per cent in the control group.

Hibbs, Day, Jung and Brady [68] report experience with the use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfapyridine in the treatment of gonorrhea in the male. Both drugs are effective agents in the treatment of gonorrhea. Clinical symptoms of the patients whose course was followed throughout the administration of chemotherapy subsided earlier when sulfapyridine was employed than when sulfathiazole was employed. The percentage of failures was greater when sulfapyridine was used (17.5) than it was when sulfathiazole was the drug employed (5.26). Clinical observations in 378 cases and

68. Hibbs, D. K.; Day, A. A.; Jung, R. W., and Brady, J. M.: Preliminary Report on the Use of Sulfapyridine and Sulfathiazole in Gonorrhea, J. Urol. **45**: 727-732 (May) 1941.

studies of the blood and the urine in a limited number of cases indicated that sulfathiazole is much less toxic than sulfapyridine. Poor cooperation of patients probably accounts for the large number of cases in which there was a lapse after good results had once been obtained. Lack of symptoms referable to chemotherapy is suggested as the reason for this negligence.

Carroll, Kappel and Lewis [69] state that sulfathiazole is an effective and safe drug in the treatment of staphylococcic infections of the urinary tract. It is readily absorbed when taken by mouth and is eliminated rapidly, mostly through the kidneys. The amount absorbed when the drug is given by rectum is too small to be therapeutically valuable. The rate of absorption from the spinal fluid as compared with that of absorption from the blood is about 4 to 1. A low concentration of the drug in the blood indicates rapid absorption, and if the patient is not recovering rapidly enough, the dosage may be materially increased. Patients receiving the drug should be seen at least every forty-eight hours, so that the physician may inquire concerning symptoms and observe carefully the skin, scleras and the gross appearance of the voided urine. Cloudy urine, oliguria and decreasing renal function should be recognized as serious warnings of temporary renal damage.

HYPERPLASTIC LESIONS OF THE URINARY TRACT

Stirling and Ash [70] report 21 cases of hyperplastic lesions of the urinary tract.

Hematuria, dysuria or frequency of urination was found in every instance and was usually severe.

Three of the patients had concomitant cysts and carcinoma of the bladder.

Brunn's follicles or nests are invaginations or extensions of surface epithelium, and their subsequent fate depends on whether the epithelial metaplasia progresses to a squamous or a glandular type.

Follicular cystitis is a nonspecific entity, common in any chronic infection.

Several hyperplastic forms of cystitis may be found in the bladder at the same time.

Stirling and Ash describe for the first time a lesion termed "papillary hyperplasia." It may combine one or more features of the other types and is important, since it may simulate tumor.

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69. Carroll, G.; Kappel, L., and Lewis, B.: Sulfathiazole and the Staphylococcus in Urinary Infections, J. Urol. **45**:770-779 (May) 1941.

70. Stirling, W. C., and Ash, J. E.: A Clinicopathologic Discussion of Hyperplastic Lesions of the Urinary Tract, South. M. J. **34**:358-364 (April) 1941.

VULVAR FUSION

Taylor [71] reports 2 cases of labial fusion in which the predominating symptoms were urologic. In the first case acquired fusion of the labia majora occurred in an adult woman; it was probably initiated by mechanical irritation. In the second case congenital fusion of the labia minora afflicted a child 7 years of age who was forced to use the vagina as a urinary reservoir.

Partial congenital fusion is probably not uncommon; it may play a definite part in the production of urinary symptoms. Such an anomaly among children should be looked for as a possible cause of infections and of anomalies of the upper part of the urinary tract as well as of such symptoms as frequency of urination, enuresis and incontinence.

INTRAVENOUS FLUID THERAPY

Murphy [72] states that clinical observations teach that some patients who have compensated cardiac lesions tolerate well large quantities of fluid, while others who have cardiac lesions of the same kind respond badly. There is no test that will enable the physician to determine beforehand whether a given patient will respond favorably to fluid therapy. Every patient should be thoroughly examined to determine the presence or absence of organic defect. If such a defect is present, regardless of the state of compensation, fluids should be administered in small volume. These should preferably be isotonic, and, most important of all, they should be administered slowly.

Patients not suffering from heart failure will tolerate fluids given in amounts up to 3,000 cc. per day, even when dehydration is absent.

The danger of the intravenous injection of fluid arises when the fluid is given thus to a patient who has an unrecognized cardiac defect and when large quantities of fluid are administered more rapidly than usual. The volume of fluid, the hypertonicity of the solution and the speed at which injection is carried out are important factors in the precipitation of heart failure.

Although many older persons tolerate the intravenous administration of fluids well, it should be remembered that occasionally some do not.

The main safeguard in the intravenous administration of fluids is a good condition of the cardiovascular system. Sufficient examination of the cardiovascular system may be made without special laboratory aids; nothing more than a careful clinical study at the bedside is required.

A study of the hematocrit determinations, the plasma protein, the venous pressure and the vital capacity is of great importance in deciding

71. Taylor, W. N.: Vulvar Fusion: Two Cases with Urological Aspects, J. Urol. **45**:710-714 (May) 1941.

72. Murphy, F. D.: The Response of the Cardiovascular System to Intravenous Fluids, J. Urol. **45**:654-663 (May) 1941.

the kinds and quantities of fluids to be administered and the rate of injection, but it does not help much in discerning the ability of the cardiovascular system to accommodate fluids.

The indiscriminate intravenous administration of fluids should be discouraged, and fluids should be given intravenously only when necessary. The established rules concerning the nature, the amount, the speed and the method of giving fluids should be strictly observed.

CHLOROMA OF THE UROGENITAL ORGANS

Mertz [73] states that chloroma is a primary disease of the bone marrow characterized by secondary green tumors which are situated throughout the body and which develop in the presence of a rather constant blood picture, that of a myeloblastic type of leukemia.

Chloroma is of especial interest to the urologist because of the frequency with which it affects the urogenital organs. In a series of 130 children with chloroma, some portion of the urogenital tract was invaded in more than 46 per cent. In 34 per cent of the patients there were chloromatous changes in the kidneys, but in only 2 per cent were there similar deposits in the bladder.

Mertz reports the cases of 2 girls with the acute myelogenous leukemia type of the disease. Chloromatous changes were present in the kidneys and the bladder of each patient, and in the ovary of 1.

Causation of the disease is not known.

No bodily tissue is immune to invasion by chloroma. Some portion of the skeletal system of almost every patient is diseased. Mertz cites Rothschild's review of the literature in which it was found that the bones of the skull had been invaded in 73 per cent of the cases.

In cases of renal chloroma both kidneys are usually diseased. Most often the size and the shape of the kidneys are but little altered; yet in some cases large renal tumors are present. The surface of the kidney may be irregular because of the presence of portions of greenish tumor tissue as large as peas on the surface.

Invasion of the renal parenchyma by chloroma is characterized by diffuse, or foci-like, myeloid metaplasia. The infiltrative lesion predominates and is more marked about the vascular channels. Occasionally, the tubules and the glomeruli seem to be embedded in the neoplastic mass, the glomeruli appearing shrunken. The myeloblastic cells do not as a rule invade the urinary channels of the kidney.

The gross picture of the cut surface of the kidney showing the diffuse infiltration type of chloroma is that of a diffuse green triangle-shaped

73. Mertz, H. O.: Chloroma of the Urinary Organs: Report of Two Patients, Each with Involvement of the Kidneys and Bladder, Tr. Am. A. Genito-Urin. Surgeons **33**:191-203, 1940.

patch or patches with the base or bases situated near the capsule; in some cases the parenchyma may be invaded by linear infiltrations of the chloromatous tissue.

The pelvic mucous membrane may present slightly elevated gray-green portions of chloromatous tissue. These may occur singly or in groups.

The lesion in the bladder in cases of chloroma may be diffuse infiltration of the wall of the bladder (often widespread), or it may be invasion of the wall of the bladder by foci of tumor tissue.

The diffuse type of invasion occurs most often in cases of chloroma in which myeloblastic tissue is present in the testis. It is not uncommon for a large portion of the testis to be involved.

The cause of the green color is not certainly known. Various explanations based on degeneration of the characteristic cells known to be present in chloroma have been proposed, but none have been generally accepted. Mertz quotes Askanazy's opinion that "the chloromata contain a pigment elaborated by a family of cells originating from the myeloid system." However, this accounts for the green color only in this disease, and the existence of Askanazy's crystals has been questioned.

Chloroma occurs more often among children than among others. Burgess found 23 years to be the average age of all patients, and Foot and Jones state that the average age of young men with the disease is 18.8 years. Seventy per cent of Atkinson's patients were men. The disease runs a rapid course, and death occurs within from a few months to a year and a half.

The clinical course of chloroma is rapidly progressive and ends in death. No method of treatment known at present seems to influence the downward course of the patient in any marked degree. Treatment has been principally supportive.

RETROPERITONEAL TUMORS

Wishard [74] states that the high incidence of abnormality of the urinary tract caused by retroperitoneal tumors warrants careful urologic investigation in every case in which the condition is suspected. The site and the tissue of origin vary widely.

Retroperitoneal tumors which affect the urinary tract are those involving the autonomic nervous system, angioma, lipoma, sarcoma, postperitoneal metastasis from primary lesions situated elsewhere and adenopathy incidental to systemic glandular disease.

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74. Wishard, W. N., Jr.: Retroperitoneal Tumors and the Urinary Tract, Including Case Report of Spontaneous Perirenal Hemorrhage, Tr. Am. A. Genito-Urin. Surgeons **33**:43-56, 1940.

These tumors may alter the urinary tract by pressure, obstruction, displacement, compression, distortion, invasion, inclusion hemorrhage or sepsis.

Spontaneous perirenal or retroperitoneal hemorrhage is rare. It may be caused by lesions in or outside the kidney. The correct diagnosis of spontaneous perirenal hemorrhage is difficult, and it rests on pain in the renal fossa, syncope caused by concealed hemorrhage and a mass of increasing size. Cystoscopy, pyelography and paracentesis may contribute important diagnostic data but should be used with discretion. The treatment is surgical.

Wishard presents a case in which spontaneous perirenal hemorrhage due to a highly undifferentiated retroperitoneal tumor was demonstrated.

MALE CLIMACTERIC

Douglas [75] states that there is a transitional phase in the life of the adult man which may be likened to the climacteric of the adult woman. This transition occurs in the middle or late forties. The diagnosis of the climacteric in the adult man is based on urinary disturbances, malfunction of the neck of the bladder, fatigue, indecision, hot flashes, nocturnal diaphoresis, decreased libido, impending impotence and some degree of prostatic involvement.

In those cases in which no abnormality is present, the secretion of gonadal substance may be stimulated by the use of testosterone propionate in doses as small as 30 mg.

The diagnosis and treatment of the transitional phase in adult male life have demonstrated that testosterone propionate is a valuable addition to the urologist's armamentarium.

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75. Douglas, R. J.: The Male Climacteric: Its Diagnosis and Treatment, J. Urol. **45**:404-410 (March) 1941.

Obituaries

DEAN DEWITT LEWIS, M.D.

1874-1941

After many months of suffering and disability, Dean Lewis died at his home in Baltimore on Oct. 9, 1941. Although his large group of friends are saddened by his loss, they must feel that he has been released from a trying and hopeless situation. As he passes from the scene, personal memories of his character, his loyalty to his country and to his friends, as well as of his great ability as a surgeon, teacher and investigator, crowd before one. Certainly no surgeon of his generation was richer in friends, and I can think of no finer epitaph as the last bell is sounded. Honors and position came to him in generous portions, and he enjoyed and prized them; but no honor ever changed his sense of the value of the homely virtues of life, and no position ever tempted him to overlook the many friendships he had made in almost every walk of life. To the many who have shared with him his enthusiasm for sports and his love of a good game and who have experienced his infectious laugh at a good story there comes a conviction that the world is a better and happier place for having had in it their friend, Dean Lewis. He will be sadly missed by all, but his spirit and his enthusiasm for good surgery will be carried on in many parts of the country and in many medical schools by the men who were fortunate enough to have come under his tutelage.

Dean DeWitt Lewis was born in Kewanee, Ill., on Aug. 11, 1874. After receiving his A.B. from Lake Forest College and his M.D. from Rush Medical College, he interned at Cook County Hospital. From 1900 to 1903, he worked as a teacher and investigator in the department of anatomy of the University of Chicago with Bensley; during this period he did six months of graduate study at the University of Leipzig with Spalteholz. He then returned to Rush Medical College and the Presbyterian Hospital, where he quickly gained a reputation as an inspiring teacher of surgical anatomy and clinical surgery and at the same time contributed a large amount of original work in the field of surgery and surgical pathology.

He recognized that it is important to the development of young men that they be given opportunities for study and investigation, and he constantly stimulated his associates. His memory of facts and people was phenomenal, and his clinics were largely attended because of his broad knowledge of the clinical subject as well as of the correlated fundamental sciences involved, which included the medicohistorical aspect. In addition to rare qualities of mind he always had the right human touch; this

was constantly in evidence in his interest in his patients and associates as persons. Such a combination is irresistible, and soon Dean Lewis not only had a large surgical practice but was much sought after as a consultant and as a speaker at medical meetings, to which he gave generously of his time and talents. In 1920 he became professor of

DEAN DeWITT LEWIS, M.D.
1874-1941

surgery at Rush Medical College and shared with Bevan the burden of teaching and directing surgical activities.

Having had many opportunities to head the departments of surgery of various medical schools, he accepted the professorship of surgery at the University of Illinois College of Medicine in 1925, but a few months later he went to Baltimore as professor of surgery in Johns Hopkins Medical School as successor to Dr. William S. Halsted. His interest

during all his years as a teacher in the development of his residents and associates has resulted in the type of training that has fitted many of them to occupy positions of importance in teaching institutions in many parts of the country.

Dean Lewis was particularly interested in the establishment of a surgical journal in which the investigative work of young surgeons throughout the country would receive early publication. He was therefore much pleased to become the first editor of the ARCHIVES OF SURGERY, which he lived to see become one of the significant surgical journals of the country. He became editor also of the widely used "Practice of Surgery," published by Prior, and at the same time edited the *International Surgical Digest.*

He was always actively interested in organized medicine and the scientific societies to which it has given rise and which have had so great an influence on the diffusion of sound knowledge. From the beginning of his career in Chicago he was an active member of the Chicago Surgical Society and the Chicago Pathological Society, and he soon became a member of many national and international organizations. Among other organizations, he was a member of the American Surgical Association, the American Association of Anatomists, the American Physiological Society, the Society of Clinical Surgery, the Interurban Surgical Society, the Southern Surgical Association, the American College of Surgeons, the Royal College of Surgeons (Ireland), the Royal Australian College of Surgeons, Societá Medico-Chirurgica di Bologna, as well as an Ausserordentliches Mitglied der Deutschen Gesellschaft für Chirurgie, and a foreign member correspondent of the Société des chirurgiens de Paris. In 1933 he was President of the American Medical Association and for several years was a member of the Council on Medical Education and Hospitals. In 1933 he was made an honorary doctor of science by the National University of Ireland.

When the first World War threatened to involve the United States, Dean Lewis organized Base Hospital No. 13 at the Presbyterian Hospital, Chicago, and took it to France in May 1918. He was detached from it and made commanding officer of Evacuation Hospital No. 7. He saw much active service at Chateau-Thierry, St. Mihiel, in the Champagne and finally, just before the armistice, at Staden, Belgium. For the efficiency of his organization and the quality of his work done under difficult conditions, he was promoted to the rank of lieutenant-colonel and given the distinguished service medal by the United States government.

His life was notable and happy. He was a positive character and always took a position on questions that seemed important. His sound surgical judgment played a considerable role in promoting good surgery wherever he worked. He leaves many friends who will never forget him.

VERNON C. DAVID, M.D.

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